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Research Article

Assessment of The Risk Factors for Statin-Related Myopathy in the Indian Population

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Abstract: Statins are widely used hypolipidemic drugs with limitations due to myopathy. Several comorbid factors act as predisposing factors for statin-related myopathy (SRM) and are rarely studied in the Indian population. In this study, we aim to understand the various risk factors involved in the occurrence of SRM, which may give insight towards the management of statin intolerance. A cross-sectional and non-interventional clinical study with 700 subjects, both statin and non-statin users, was conducted. Subjects were enrolled after ethical approval and informed consent. Information on case report forms and blood samples for clinical chemistry investigations were collected. SPSS version 21 was used to collect and analyze data. Based on statistical analysis, we found myopathy in statin users (19%), nonstatin users (11%), and total subjects (16%), respectively. No significant association of myopathy was observed with the female sex, differences in food habits, physical activity, alcohol intake, or comorbid factors like diabetes and hypertension. Smoking is associated with myopathy in pooled subjects, whereas age (>60) is associated with myopathy in statin users. Slight differences in mean values of bilirubin and alanine transferase were observed between myopathic and non-myopathic subjects. Therefore, the study demonstrates that smoking is related to myopathy regardless of statin usage. Statin users over 60 were shown to be at a greater risk for myopathy than non-statin users.

Keywords: Statin-induced myopathy, atorvastatin, statin risks, smoking.

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1. INTRODUCTION

Statins are the most popular medicaments in the category of hypolipidemic. However, myopathy remains one of the significant limitations of statin use. [1] The term "statin-related myopathy (SRM)" is generally used for a range of muscle symptoms, which include mild muscle weakness to life-threatening necrotizing myopathy. [2] Recently, initiatives to standardize the terminology used in statin-related myopathy (SRM) have been made. Accordingly, the SRM is categorized into seven phenotypic categories, with the levels of serum creatinine kinase serving as the primary descriptor for each group (CK). [3] Although these muscular complaints are frequently disregarded due to age-related factors, they impact a patient's quality of life. They may even have severe consequences. [4] It should be noted that according to one study, 44.4% of statin discontinuers cited muscle pain as the primary reason. [5] Cerivastatin has been banned from the market due to its adverse effects on rhabdomyolysis. [6] The definitive mechanism of statin-induced myopathy is still under investigation. Many hypotheses have been proposed to understand the mechanism. Some of these include isoprenoid depletion due to inhibition of HMG-CoA reductase (3-hydroxy-3-methylglutaryl-coenzyme A reductase) by statins, lack of coenzyme Q10, disruption of calcium signalling pathways[7], etc. Aside from these molecular hypotheses, comorbid factors (age, lifestyle disorders, alcohol and smoking, vitamin D deficiency, drug interactions, and so on) play a significant role in the occurrence of myopathy. [8,9] Few risk factors can cause myopathy and pose a greater risk. Among them, age and vitamin D deficiencies are often quoted. Age is considered one of the significant risk factors and is not modifiable in the development of SRM.[10] Elderly people are usually subjected to sarcopenia, which, combined with other factors, including statin use, may increase the probability of experiencing myopathy. Sometimes, in older people, it may also happen to be "inclusive body myositis," which progresses slowly and painlessly initially but can have devasting effects later. [11] Having a low body mass index is also viewed as a potential contributor to the development of this condition. [12] Other risk factors include indulgence in alcohol and smoking, though the former is reported to pose a greater risk. [13, 14] Studies suggest that participating in at least one physical activity daily improves muscle strength and minimises the risk of myopathy. [15] However, a few reports claim overindulgence in physical activity can also cause myopathy. [16] Vitamin D deficiencies have also been linked to myopathy. [17] Comorbid conditions like diabetes mellitus, hypertension, hypothyroidism, kidney failure, etc., are also involved in SRM. [18] When compared to the potential benefits of statin therapy, the risk of myopathy is typically outweighed by these benefits. Most of these factors that increase the likelihood of developing SRM can be altered through dietary and nutritional adjustments, like supplementation of vitamin D3 and phosphorous, lifestyle modifications etc. [19] Although many factors are involved in predisposing to SRM, in this study, we tried to explore a few of them and their relationship with SRM in the Indian population to provide practical insights for better management of statin use.

2. METHODOLOGY

This is a clinical, cross-sectional, and observational study conducted in one of the tertiary care hospitals in Hyderabad, Telangana. This study was initiated after receiving approval from the Ethical Committee at the study site (ECR/300/INST/AP/2013).

2.1. Selection of subject

800 subjects were initially screened based on selection criteria. However, only 700 subjects were enrolled for future investigations.

The exclusion criteria include 1) subjects with uncontrolled diabetes mellitus based on the past six months' blood sugar reports, 2) kidney failure, 3) low potassium levels, 4) high uric acid levels, 5) subjects with infections and injuries, 6) Pregnant and lactating females were also excluded.

The inclusion criteria include subjects of either sex, age above 20 years, and willingness to participate in the study, which did not fall under the exclusion criteria. Subjects were enrolled after receiving written, informed consent. Blood samples were drawn following suitable precautions.

2.2. Definition of myopathy

In the current study, “myopathy” is used as a general term for various symptoms of pain related to skeletal muscle based on subjective assessment and irrespective of creatinine kinase values.

2.3. Case report form

A case report form was developed per the standard procedures of WHO, which is then pretested and modified accordingly. The case report forms included information on anthropometric measurements, present and past medication, food habits, physical exercise, smoking and alcohol use, comorbid diseases, statin prescription with dose and duration, disorders related to myopathy, etc. The subjective assessment of myopathy is also recorded in the case report form. The physical examination further validates the personal evaluation. [20]

2.4. Clinical chemistry analysis

Clinical chemistry investigations include lipid profile tests, liver function tests (HDL (high-density lipoprotein), LDL (low-density lipoprotein), triglycerides, and total cholesterol), kidney function tests (serum creatinine, blood urea nitrogen, uric acid, albumin, and urea), serum calcium, serum phosphorous, and creatinine kinase). The auto analyzer (Roche COBAS) was used for these investigations. In addition, serum levels of vitamin D3 were investigated by HPLC (high-pressure liquid chromatography). [21] All the investigations were done in duplicate to avoid inconsistency.

2.5. Data analysis

The data was compiled using Microsoft Excel, and further analysis was done by SPSS (Statistical Package for Social Sciences, version 21, Chicago, IL). An independent t-test was used to compare various biological parameters. To compare nominal variables, a chi-square test has been performed. Correlation and regression tests were applied to obtain the relationship between different risk variables as per the application. In regression analysis, a confidence interval of 95% is considered. All the statistical tests were considered significant at a p-value of 0.05.

3. RESULTS

In this clinical study, a total of 700 subjects were investigated to assess the risk factors associated with myopathy. Among them, 35% are males, and 65% are females. Due to the high number of women in the outpatient department at the study site, there are more women than men in the study. Around 16% of the total subjects were found to be myopathic. In this study, we initially tried to understand the significance of various parameters in causing myopathy. Therefore, we pooled the subjects of statin and non-statin users, and various demographic and clinical parameters were compared between the myopathic and non-myopathic groups. More females were found to be myopathic as compared to males. However, the results were not found to be significantly different on statistical analysis. No significant differences were observed between the myopathic and non-myopathic groups concerning age (p-value of 0.42) and BMI (body mass index) (p-value of 0.83). No significant influence on myopathy was observed due to the difference in food habits (p-value = 0.35). Although indulgence in alcohol was not found to influence myopathy, smoking was significantly associated with the occurrence of myopathy (p = 0.01). Comorbid conditions like diabetes mellitus and hypertension are not significantly associated with myopathy. However, using statins has significantly increased the risk of myopathy, with a p-value of 0.01. (Table 1).

Table 1: Comparison of various demographic characteristics between myopathic and non-myopathic subjects.

S.no.	Parameter		Myopathic (%)	Non-myopathic (%)	P value*	OR*
1.	Sex	Male	12.6	87.4	0.13	1.4
		Female	17.1	82.9		
2.	Age	≤60 years	15.1	84.9	0.42	1.19
		≥ 60 years	17.5	82.5		
3.	BMI	<18.5 kg/m2	14.3	85.7	0.83	0.93
		18.5–25 kg/m^2	15	85		
		>30 kg/m^2	13.8	86.2		
4.	Food habits	Vegetarians	18.4	81.7	0.35	1.02
		Non-vegetarians	15.5	84.5		
5.	Alcohol use	Alcoholic	12.2	81.8	0.40	1.2
		Non-alcoholic	17.1	82.9		
6.	Tobacco use	Current Smokers	25.9	74.1	0.01	0.58
		Non-smokers	13.8	86.2		
7.	Diabetes mellitus	Diabetic	19.2	80.8	0.90	0.9
		Non-Diabetic	18.2	81.8		
8.	Hypertension	Hypertensive	18.6	81.4	0.77	1.1
		Non-Hypertensive	20	80		
9.	Statin use	Statin users	19.1	80.9	0.01	0.55
		Non-statin users	11.7	88.3		

**Chi-square analysis compares nominal variables between a myopathic and non-myopathic group. P-value <0.05 is considered significant. **OR refers to the Odds Ratio calculated at a 95% confidence interval.*

The table 1 shows that statin use and smoking were risk factors significantly associated with myopathy. Biochemical parameters are compared between myopathic and non-myopathic subjects, with results shown in Table 2. There was no significant difference in lipid profile parameters such as HDL, LDL, and total cholesterol values. Although the mean is in the normal range, a substantial difference in bilirubin values was observed between myopathic and non-myopathic subjects. Alanine aminotransferase values were also significantly different in myopathic and non-myopathic subjects. The mean values of creatinine kinase were higher in myopathic patients than in non-myopathic patients. However, no statistical significance was observed. (Table 2).

Table 2: Comparison of various biochemical parameters between myopathic and non-myopathic subjects

S.No.	Parameter	Myopathic (Mean±SE)	Non-myopathic (Mean±SE)`	p-value*
1.	HDL cholesterol (mg/dl)	35.62±0.85	35.94±0.47	0.78
2.	LDL cholesterol (mg/dl)	99.32±4.06	100.24±1.87	0.84
3.	Triglycerides (mg/dl)	196±10.5	201.11±5.2	0.67
4.	Total Cholesterol (mg/dl)	167.27±1.9	166.27±1.9	0.85
5.	Serum Calcium (mg/dl)	9.2±0.08	9.1±0.06	0.56
6.	Serum Phosphorous(mg/dl)	3.63±0.04	3.63±0.07	0.95
7.	Bilirubin (mg/dl)	0.41±0.02	0.47±0.01	0.06
8.	Aspartateaminotransferase (IU/L)	21.42±0.86	21.42±0.55	0.9
9.	Alanine aminotransferase (IU/L)	16.82±0.7	19.85±0.59	0.03
10.	Alkaline phosphatase (IU/L)	99.46±3.39	94.5±1.55	0.20
11.	Serum Creatinine(mg/dl)	0.64±0.02	0.722±0.22	0.16

12.	Serum Uric acid(mg/dl)	4.14±1.45	4.86±0.34	0.36
13.	Serum Urea(mg/dl)	20.99±0.84	23.64±0.69	0.1
14.	Creatinine Kinase (U/L)	104.04±3.8	90.12±5.62	0.12
15.	25 OH Vitamin D3 (ng/µl)	26.50±2.44	26.19±2.7	0.96

*Independent 't' test analysis compares continuous variables between myopathic and non-myopathic groups. p-value <0.05 is considered as significant. Comparing myopathic and non-myopathic groups, we found significant differences in bilirubin and alanine transferase values. The probability of various risk factors predisposing to myopathy in statin users was analysed using regression analysis. It was found that the subjects with ages greater than 50 years are at 2.13 times more risk for statin-related myopathy, with a level of significance of 0.01. Although alcohol and smoking are usually related to myopathy, we found no significant increase in the risk of SRM. Vitamin D deficiency also did not show a significant increase in the risk of myopathy in statin users. (Table3)

Table 3: Risk factor estimation among statin users

S.No.	Parameter	Myopathic (%)	Non-myopathic (%)	OR (95% CI)	p-value*
1	Female sex	19.3	80.7	1.3	0.35
2	Age (>60 years)	24.6	75.4	2.13	0.01
3	Alcohol	20.4	79.6	0.98	0.95
4	Smoking	28.8	71.2	0.71	0.24
5	Diabetes	19.2	80.8	1.05	0.92
6	Hypertension	18.6	81.4	1.3	0.92
7	25 OH vitamin D3 deficiency (<12ng/ml)	18.7	81.3	1.2	0.55

**Regression analysis is performed to assess the risk of the above variables in the occurrence of myopathy. p-value <0.05 is considered as significant. In addition, statistical analysis shows that age is significantly associated with myopathy in statin users.*

4. DISCUSSION

Heart disease and stroke remain the leading causes of mortality, and statins are the best-studied medications for lowering the risk of cardiovascular diseases. Although they are well tolerated, myopathy remains a significant adverse effect. [1] As the mechanism of SRM has not yet been elucidated, understanding the role of predisposing factors helps better manage SRM. Many factors have been discovered to play a role in predisposing to SRM. [10] In this study; we found that regular smoking increases the risk of myopathy. While many studies have linked vitamin D deficiency to myopathy, we found no such link. [19,22] The risk of SRM is increased by 2.13 times in people over 50 who use statins. Smoking is usually related to chronic obstructive pulmonary disorders. [23] But even before affecting the lungs, smoking is reported to cause skeletal muscle dysfunction, which in turn causes myopathy. [14] Cigarette smoking causes muscle wasting, mitochondrial dysfunction, and oxygen deficiency, all of which contribute to myopathy. [14] Our study results also align with these studies, where the risk of myopathy increases with cigarette smoking regardless of statin use. [23] However, in statin users, smoking is not significantly associated with SRM. Our study results are supported by another study conducted in the Indian population where SRM is not associated with smoking in statin users. [24] Age is one of myopathy's significant, non-modifiable risk factors.[25] In this study, we found that age is substantially linked with myopathy in statin users, with a 2.13-fold increased risk in subjects older than 60. Research conducted by Schech et al. revealed that people aged 65 and older experience a fourfold increased risk of myopathy compared to younger participants. [10] This may be due to age-related changes in the body and sometimes an increase in the frequency of comorbidities. [11] Muscle wasting is also seen in elderly patients. [25] However, in pooled subjects, we did not observe a significant increase in the risk of myopathy with increasing age. This could be because, compared to statin users, non-statin users have fewer complications. The female gender is also usually associated with SRM and myopathy. [26] However, in this study, we did not find a significant association of female gender with myopathy in both pooled subjects and statin users. Vitamin D deficiency is another risk factor often associated with myopathy. Few studies supported the role of vitamin D deficiency in myopathy through supplementation studies. [27] However, in this study, we did not find a significant association between pooled subjects and Statin users. The relationship between stain-induced myopathy and vitamin D deficiency is sometimes referred to as far-fetched, and definitive evidence is lacking. [19] Therefore, at this juncture, we cannot comment on the use of vitamin D supplementation to manage or alleviate statin-related myopathies. Various biological parameters are compared between myopathic and non-myopathic groups. However, we did not find a significant difference in means between myopathic and non-myopathic groups for most of them. Although the mean values of bilirubin and ALT are in the normal range, a significant difference is observed between myopathic and non-myopathic groups. Both of them are liver function tests. However, further investigation is necessary to conclude their relationship. [28] Though not significant, differences in creatinine kinase values were observed between myopathic and non-myopathic groups. This may be because creatinine kinase levels are related to myopathy. [3,29]

5. CONCLUSION

Within the scope of this investigation, several potential risk factors for myopathy were explored. Smoking is one of the risk factors for myopathy, and a significant association between myopathy and smoking was found regardless of statin use. Also, people over 60 under statin therapy had a higher risk for myopathy than those without. Other risk factors did not show significant associations in this study. Although vitamin D deficiency is commonly associated with myopathy, neither statin nor non-statin users be at risk.

6. AUTHOR CONTRIBUTION STATEMENT

Dr B. Dinesh Kumar conceptualized and designed the research. Project. Kiranmayee Ale executed the project. Prof. Shyam sunder guided the research and writing the article.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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