Vocal tract symptoms: Severity and frequency in patients on statins

Abdul-Latif Hamdan, MD, MPH, FACS; Marc Mourad, MD; Ghina Fakhri, BS; Doja Sarieddine, BS; Elie Khalifee, MD; Sami T. Azar, MD

Abstract

The objective of the study was to analyze the frequency and severity of vocal tract symptoms in patients on statins. A total of 73 patients were enrolled in this study, 44 patients who were taking statins and 29 controls not taking statins. The severity and frequency of vocal tract discomfort was assessed using the Vocal Tract Discomfort scale. The most frequent vocal tract symptom in patients on statins was dryness followed by tightness and lump sensation. The difference in the mean of the total score and in the mean frequency of any vocal tract symptom was not significant between patients taking statins and controls. The most severe (highest mean values) vocal tract symptom in patients taking statins also was dryness followed by tightness and lump sensation. The difference in the mean of the total score and in the mean severity of any vocal tract symptom between patients taking statins and controls was not significant. This study failed to demonstrate a higher prevalence or severity of vocal tract symptoms in patients receiving statins. Despite the lack of a significant difference in the means of vocal tract discomfort symptom frequency and severity, this study carries clinical significance when considering that a higher prevalence and severity of vocal tract discomfort symptoms should alert physicians to the possible development of statin-induced myotoxicity in the laryngopharyngeal complex.

Introduction

The statin class of cholesterol-lowering medications has truly revolutionized preventive cardiology. Since they were first introduced in 1987, the use of statins has grown remarkably, reaching more than 100 million prescriptions per year.[1] Statins, like other medications, have side effects, and myopathy seems to be the most common one.[2] Myotoxicity usually occurs within the first month of treatment and is more common in women than in men and in patients older than 75 compared with their younger counterparts.[3-6]

The clinical spectrum of myopathy ranges from an asymptomatic increase in the concentration of creatine kinase to myalgia, myositis, and rhabdomyolysis. The incidence of myalgia is reported to be 1.5 to 3% in randomized, controlled trials and up to 10 to 13% in prospective clinical studies.[2,4,7,8] Patients taking statins may complain of muscle weakness, cramps, or nonspecific muscle aches. These side effects, although subclinical, must not be taken lightly as they may limit physical activity, affect quality of life, and reduce adherence to statin treatment, thus depriving patients of the clinical benefits.[9,10]

Given that the laryngopharyngeal complex is a musculoskeletal structure prone to the same statin-induced myotoxicity as the remaining musculoskeletal structures in the body, the purpose of this investigation is to analyze the frequency and severity of throat symptoms in patients on statins using a validated questionnaire, the Vocal Tract Discomfort scale. We hypothesize that the frequency and severity of throat symptoms are greater in patients receiving statins compared with subjects not taking statins.

Patients and methods

A total of 73 patients (44 statin recipients and 29 controls not taking statins) agreed to participate in this study after having read and signed the informed consent approved by the Institutional Review Board. Patients underwent fiberoptic or telescopic laryngeal examination before their enrollment in this study. Exclusion criteria included recent history of laryngeal manipulation, upper respiratory tract infection, and/or abnormal laryngeal findings.

Demographic data included age, sex, Reflux Symptom Index (RSI) as established by Belafsky et al, and the dosage and duration of statin therapy.[11] The severity

From the Department of Otolaryngology–Head and Neck Surgery (Dr. Hamdan, Dr. Mourad, Mrs. Sarieddine, and Dr. Khalifee), the Department of Medicine (Ms. Fakhri), and the Department of Internal Medicine (Dr. Azar), American University of Beirut Medical Center, Lebanon.

Corresponding author: Sami T. Azar, MD, Internal Medicine Department, American University of Beirut, PO Box 11-0236, Beirut, Lebanon. Email: sazar@aub.edu.lb

Table 1. Comparison of the means of vocal tract discomfort frequency of symptoms between statin recipients (n = 44) and controls (n = 29)

	Patients		Controls		*p* Value
	Mean	Range	Mean	Range	
Burning	0.14 ± 0.668	0-4	0.34 ± 0.974	0-4	0.170
Tight	0.34 ± 1.140	0-6	0.17 ± 0.658	0-3	0.529
Dry	0.59 ± 1.515	0-6	0.38 ± 1.208	0-5	0.503
Aching	0.23 ± 1.054	0-5	0.14 ± 0.743	0-4	0.793
Tickling	0.14 ± 0.554	0-3	0.07 ± 0.371	0-2	0.539
Sore	0.07 ± 0.452	0-3	0.14 ± 0.743	0-4	0.750
Irritable	0.14 ± 0.554	0-3	0.00 ± 0.00	0-0	0.154
Lump	0.32 ± 1.073	0-5	0.31 ± 0.891	0-4	0.596
Total	1.95 ± 4.979	0-26	1.55 ± 3.813	0-20	0.518

and frequency of vocal tract discomfort symptoms were assessed subjectively using the Vocal Tract Discomfort scale first described by Woźnicka et al.[12] The Vocal Tract Discomfort scale is a questionnaire that assesses both the severity and frequency of eight commonly encountered vocal tract symptoms (lump sensation, burning, itching, tightness, dryness, aching, soreness, and irritability) using a 0 to 6 Likert scale for each. The total score ranges from 0 to 48 for each of the severity and frequency subscales. Higher scores mean more severe and more frequent symptoms.[12]

Descriptive statistics were used to compute the means and the standard deviation of the continuous variables and the frequencies of the categorical variable. The Mann-Whitney *U* test was used to compare the means of the continuous variables between patients and controls. As for the categorical variables, the Pearson chi-square test was used to compute the *p* value, and the Fisher exact test was reported when more than 20% of the cells had a cell count <5. Statistical analysis was performed using the IBM Statistical Package for the Social Sciences software for Windows, v. 22.[13]

Results

Demographic data. The mean age of patients on statins was 54.68 ± 8.12 years, and the mean age of controls was 45.24 ± 13.69 years. The ratio of men to women was 1:1. The duration of therapy ranged from 3 to 288 months (mean: 66). Mean scores on the RSI in patients taking statins and in controls were 6 and 7, respectively. Eight of 44 (18.2%) patients taking statins had an RSI score >13 compared with 7 of 29 (24.1%) controls.

Frequency of vocal tract discomfort symptoms. The most frequent vocal tract symptom in patients taking statins was dryness (mean of frequency: 0.59) followed by tightness (mean of frequency: 0.34) and lump sensation (mean of frequency: 0.32). The most frequent vocal tract symptom in the controls was dryness (mean frequency: 0.38) followed by burning (mean frequency: 0.34) and lump sensation (mean frequency: 0.31). The observed difference in the mean of the total score and the mean frequency of any vocal tract symptom between patients

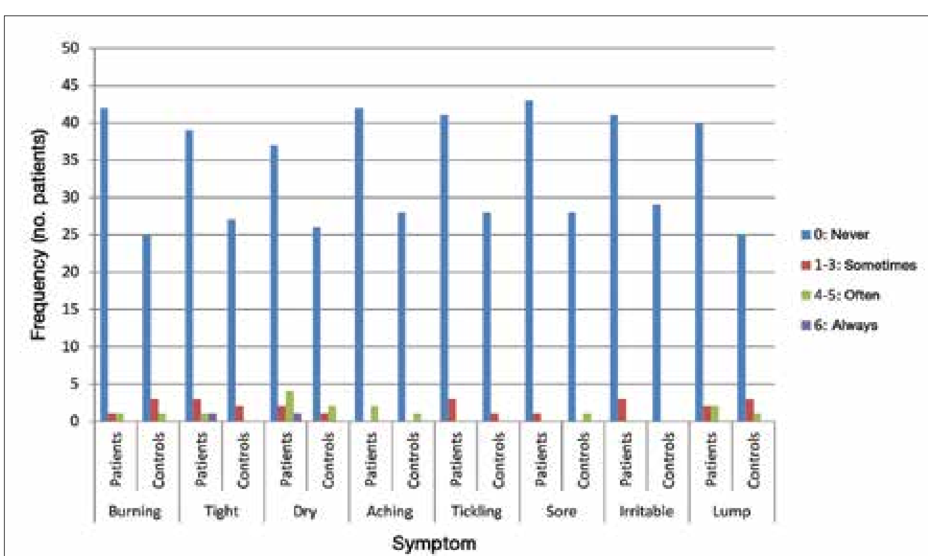

Figure 1. Bar chart compares the Vocal Tract Discomfort scale frequency *per symptom between patients and controls.*

Table 2. Comparison of the means of vocal tract discomfort severity of symptoms between stain recipients (n = 44) and controls (n = 29)

	Patients		Controls		*p* Value
	Mean	Range	Mean	Range	
Burning	0.16 ± 0.805	0-5	0.48 ± 1.299	0-5	0.163
Tight	0.36 ± 1.222	0-6	0.17 ± 0 .658	0-3	0.529
Dry	0.64 ± 1.586	0-6	0.41 ± 1.268	0-5	0.497
Aching	0.11 ± 0.538	0-3	0.14 ± 0 .743	0-4	0.844
Tickling	0.23 ± 0.922	0-5	0.07 ± 0.371	0-2	0.506
Sore	0.07 ± 0.457	0-3	0.14 ± 0.743	0-4	0.762
Irritable	0.14 ± 0.554	0-3	0.00 ± .000	0-0	0.154
Lump	0.32 ± 1.137	0-6	0.52 ± 1.430	0-6	0.519
Total	2.02 ± 4.967	0-25	1.93 ± 3.954	0-20	0.420

taking statins and controls was not significant, with a *p* value ≥0.05 (table 1).

The distribution of vocal tract discomfort symptom frequencies as *never, sometimes, often,* and *always* in both groups is shown in figure 1.

Severity of vocal tract discomfort symptoms. The highest means for vocal tract symptom severity in patients taking statins were for dryness (mean severity: 0.64), tightness (mean severity: 0.35), and lump sensation (mean severity: 0.32). The highest means for vocal tract symptom severity in controls were for lump sensation (mean severity: 0.52), burning (mean severity: 0.48), and dryness (mean severity: 0.41). The difference in the mean of the total score and the mean severity of any vocal tract symptom between patients taking statins and controls was not significant (table 2).

The distribution of vocal tract discomfort symptom severity as *none, mild, moderate,* and *extreme* in both groups is shown in figure 2.

Discussion

The mechanism of statin-induced myopathy is controversial. Several theories that revolve around the following known actions of statins exist: reduction of metabolic intermediates such as mevalonic acid, farnesol, geranylgeraniol, and ubiquinone; upregulation of apoptotic pathways; modification of chloride channel conductance; alteration of muscle membrane function; impairment of Na^+/K^+-ATPase and Na^+/Ca^+-ATPase pump function; and reduction in selenoprotein production.[13-15]

Several studies have documented that the inhibition of protein prenylation is behind the muscle injury and results in the induction of pro-apoptotic pathways. In contrast, various reports of statin-induced polymyositis, dermatomyositis, and other autoimmune diseases are in favor of immunologic and toxic mechanisms.[16] To that end, the role of statins as immune modulators is very controversial, with few reports describing statins as agents capable of inducing autoimmune disorders.[17-19]

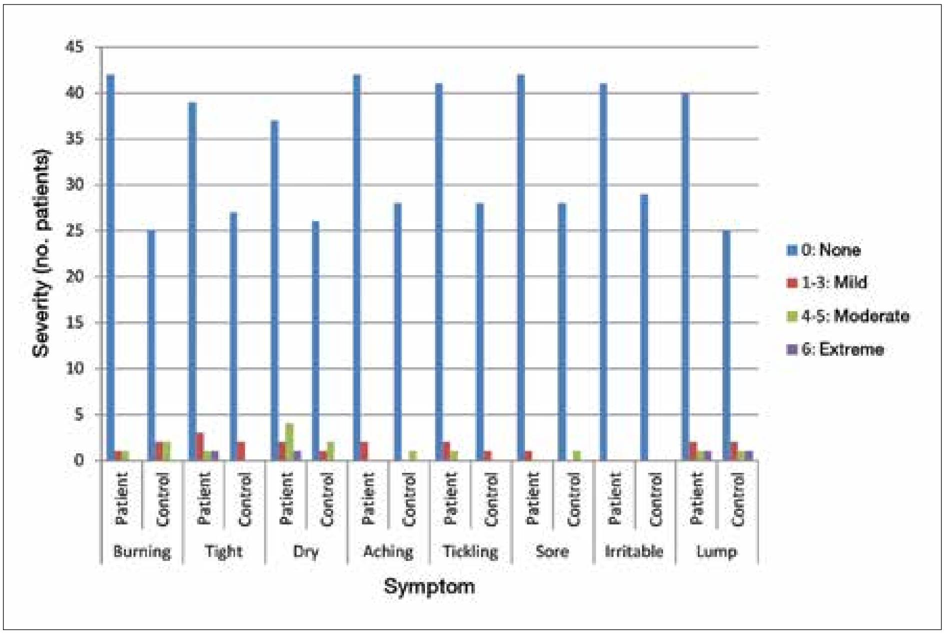

Figure 2. This bar chart compares the Vocal Tract Discomfort scale severity *per symptom between patients and controls.*

With the mechanism of myopathy still under investigation, the number of reports on the effect of statins on muscle strength and exercise tolerance is increasing.[1] The results of our investigation failed to show a significant difference in the means of the frequency and severity of vocal tract discomfort symptoms between patients taking statins compared with those not taking statins. These findings can be attributed to two factors.

First, the association between statin intake and muscle pain and weakness is controversial despite the many reports stating that adult patients taking statins are significantly more likely than the general population to report musculoskeletal pain.[20] Based on Buettner et al, patients taking statins have 50% greater odds of any musculoskeletal pain and 50 to 60% greater odds of back and lower extremity pain.[20] These results corroborate the findings of several previous observational and postmarketing surveillance studies.[4,21-23] Still, numerous randomized clinical trials showed no significant association between myalgia and statins.[24,25]

Similarly, findings regarding statin-induced muscle weakness are contradictory. Some studies showed a decline in muscle strength with statin treatment whereas others found no change or even an increase in strength.[26-31] For instance, Loenneke and Loprinzi found that statin treatment indirectly decreases muscle force by decreasing the engagement in muscle strengthening activities due to the muscle pain induced by statin therapy.[32] In contrast, Bruckert et al demonstrated that muscular symptoms are exacerbated by exercise and are more apparent in those who are physically active compared with those who are sedentary.[4]

Second, studies have shown that myopathy is related to the duration of therapy. Worth noting is that statin-induced myotoxicity is more likely to occur during the first 6 months of therapy, whereas the patients enrolled in this study were on therapy for an average of 66 months.[33]

Our study has two main limitations. First, it lacks objective measurements on a confounding disease, namely laryngopharyngeal reflux disease that may present with symptoms similar to those listed in the Vocal Tract Discomfort scale. Although the demographic data shed information on the frequency of laryngopharyngeal symptoms in both groups of patients, this investigation lacks objective measurements such as double-probe pH metry or pharyngeal impedance to either refute or confirm the presence of laryngopharyngeal reflux disease.

Another limitation is the duration of the investigation and the enrollment of patients who were on statins for an extended period. Nevertheless, this study is the first to investigate the prevalence of vocal tract discomfort symptoms in patients taking statins compared with a control group.

Despite the lack of a significant difference in the means of vocal tract discomfort symptom frequency and severity between patients taking statins and controls, this study carries clinical significance if we consider that a higher prevalence and severity of vocal tract discomfort symptoms in patients taking statins should alert the treating physician to the possible development of statin-induced myopathy.

Based on the Prediction of Muscular Risk in Observational conditions study, among the several predictors for the development of statin-induced myotoxicity are hypothyroidism, history of muscle symptoms, and/or unexplained muscle cramps.[4,5] The list has increased recently to include aging, female sex, body mass index, and intake of several medications and/or alcohol.

Conclusion

This study failed to demonstrate a higher prevalence or severity of vocal tract symptoms in patients taking statins despite the known statin-induced myotoxicity. Three possible reasons for the negative results are the small sample size, the late time of investigation that could have missed the early phase of toxicity, and the possible presence or lack of laryngopharyngeal reflux disease, an important confounding variable that should be excluded in the future using objective measures.

References

1. Sathasivam S, Lecky B. Statin induced myopathy. BMJ 2008;337:a2286.
2. Scott RS, Lintott CJ, Wilson MJ. Simvastatin and side effects. N Z Med J 1991;104(924):493–5.
3. Skilving I, Eriksson M, Rane A, Ovesjö ML. Statin-induced myopathy in a usual care setting—a prospective observational study of gender differences. Eur J Clin Pharmacol 2016;72(10):1171-6.
4. Bruckert E, Hayem G, Dejager S, et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients —the PRIMO Study. Cardiovasc Drugs Ther 2005;19(6):403-14.
5. Pasternak RC, Smith SC Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. Stroke 2002;33(9):2337-41.
6. Walsh JE, Pignone M. Drug treatment of hyperlipidemia in women. JAMA 2004;291(18):2243-52.
7. Law M, Rudnicka AR. Statin safety: A systematic review. Am J Cardiol 2006;97(8A):52C-60C.
8. Bays H. Statin safety: An overview and assessment of the data—2005. Am J Cardiol 2006;97(8A):6C-26C.
9. Chapman MJ, Carrie A. Mechanisms of statin-induced myopathy: A role for the ubiquitin-proteasome pathway? Arterioscler Thromb Vasc Biol 2005;25(12):2441-4.
10. Ballantyne CM, Corsini A, Davidson MH, et al. Risk for myopathy with statin therapy in high-risk patients. Arch Intern Med 2003;163(5):553-64.
11. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice 2002;16(2):274-7.
12. Woźnicka E, Niebudek-Bogusz E, Kwiecień J, et al. Applicability of the vocal tract discomfort (VTD) scale in evaluating the effects of voice therapy of occupational voice disorders. Med Pr 2012;63(2):141-52.

Continued on page 136