The Prevalence of Dysphonia and Dysphagia Symptoms in Patients on Statin Therapy

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Summary: Objective. To investigate the effect of statin therapy on swallowing and phonation.

Methods. A group of patients on statin therapy and another group not on statins (controls) presenting to the endocrinology clinic between January 2018 and April 2018 were asked to participate. All patients filled Voice Handicap Index (VHI-10), Eating Assessment Tool (EAT-10), and Likert scales for vocal fatigue and hoarseness. Demographic data included age, gender, allergy, and history of smoking.

Results. A total of 160 patients were recruited, 75 patients on statin therapy and 85 not on statin therapy. The mean age of the study group was 55.00 years, whereas that of the control group was 45.70 years. The mean duration of statin treatment was 74.92 months. The mean VHI-10 and EAT-10 scores were significantly higher in the statin group compared to the control group ($P < 0.05$). Although there was no significant difference in the mean Likert scale for vocal fatigue, the mean Likert scale for hoarseness was significantly higher in the statin group compared to the control group ($P < 0.05$).

Conclusion. This investigation revealed a significantly higher prevalence of laryngopharyngeal symptoms in patients on statin therapy versus a control group.

Key Words: Statin therapy−Dysphagia−Dysphonia−VHI-10−EAT-10.

INTRODUCTION

Several classes of lipid-lowering agents were developed over the past years, among which statins are considered the most effective and most commonly prescribed. The indications for statins prescription expand beyond hypercholesterolemia to include ventricular arrhythmias, idiopathic dilated cardiomyopathy, cancer, osteoporosis and diabetes.[1] Based on the American Diabetes Association, initiation of statins in diabetic patients with cardiovascular risk factors is the standard of care but nevertheless should not be based solely on a low-density lipoprotein (LDL) target level.[2] By competitively inhibiting HMG-CoA reductase**,** which is the rate-limiting step of cholesterol synthesis,[3] statins lead to an increase in LDL receptor turnover and to a decrease in very low level of LDL production in the liver.[4−6] These effects reduce the inherent risks of cardiovascular diseases and associated comorbidities.

Although statins are considered the safest lipid-lowering agents, their use confers considerable side effects that may mitigate or compromise their benefits. These include diabetes mellitus, hepatic and renal dysfunction, in addition to musculoskeletal toxicity. New-onset diabetes mellitus, though rare, has been reported following initiation of statin therapy. Several mechanisms have been suggested among which there is a decrease in coenzyme Q10 and translocation of glucose transporter 4.[7] An equally important side effect is musculoskeletal toxicity that ranges between 1.5% and 5%, and is considered the most common reason behind cessation of treatment.[8,9] Patients may present with muscle fatigue, pain, cramps, and weakness, which can be secondary to myopathy, myositis, and rarely myonecrosis.[1,8] Despite the ubiquity of reports in the literature on statin-induced myopathy and the fact that the laryngopharyngeal complex is a musculoskeletal structure, the effect of statins on swallowing and phonation has not been investigated.[10]

Dysphagia can be the result of any disruption in the swallowing mechanism leading to difficulty in deglutition of liquids and solids. At the oropharyngeal phase, any neuromuscular disorder that may be drug-induced can lead to a dysfunction in motility and ability to swallow. Similarly, phonation is the result of a delicate interaction between the nervous system and laryngeal muscles,[11] and as such any disturbance in laryngeal muscle function may result in phonatory symptoms leading to a change in voice quality.

Given the scarcity of reports on statin-induced myopathy and the laryngopharyngeal complex, the aim of this study is to investigate the prevalence of dysphonia and dysphagia symptoms in patients on statin therapy using self-reported validated questionnaires.

METHODOLOGY

After obtaining the institutional review board approval, a prospective cohort study was conducted at the American University of Beirut Medical Center from January 2018 to April 2018. Patients above 18 years of age presenting to the endocrinology clinic during that period were asked to participate. A total of 160 patients, 75 patients on statin therapy and 85 patients not on statin therapy, were recruited.

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Patients below 18 years of age or those with history of recent upper respiratory tract infection, laryngeal manipulation, and/or neurologic disorders were excluded. Demographic data included age, gender, and history of smoking.

Phonatory symptoms were assessed using the Voice Handicap Index (VHI-10) questionnaire, which is a self-reported, subjective assessment tool for dysphonia that contains a total of 10 questions, each scaled from 0 (no impairment) to 4 (maximum impairment) with a score above 11 being significant.[12] The Likert scale from 0 to 10 was used to evaluate the severity of vocal fatigue and hoarseness. Vocal fatigue was defined as increased difficulty in achieving voice projection,[13] whereas hoarseness was defined as altered voice quality, pitch, or loudness. Dysphagia was evaluated using the Eating Assessment Tool (EAT-10), which is a self-administered symptom-specific outcome instrument with a score above 3 being significant.[14] The information on the definition of vocal fatigue and hoarseness were explained to the patient before filling the questionnaires. Laryngeal examination, acoustic analysis, and functional endoscopic evaluation of swallowing were not performed given that the main objective of this investigation is to assess the prevalence of dysphonia and dysphagia using self-reported validated questionnaires. A future study that includes comprehensive voice and swallowing evaluation will be performed in the future.

Statistical analysis

Means (±standard deviation) and frequencies were calculated to describe continuous and categorical variables, respectively. Mann-Whitney *U* test was used to compare the means of the continuous variables between patients and controls. Data were analyzed using SPSS version 23 (SPSS Inc, Chicago, Illinois).

RESULTS

Demographics

A total of 160 patients were included in this study: 75 patients on statin therapy referred to as study group, and 85 patients not on statin therapy referred to as controls. The mean age of the study group was 55.00 ± 8.2 years, whereas that of the control group was 45.70 ± 12.9 years. The prevalence of smoking was 57.33% in the study group and 43.53%, in the control group. The mean duration of statin treatment was 74.92 ± 68.81 months (Table 1).

TABLE 1.
Demographics

	Statin Group ($N = 75$)	Control ($N = 85$)
Age (years)		
Mean ± SD	55.00 ± 8.20	45.70 ± 12.90
Gender (*N*)		
Male	29	27
Female	46	58
Smoking (%)	57.33	43.53
Duration of statin therapy (months)	74.92 ± 68.81	–

Self-reported measures

VHI-10 in the study and control groups

The mean VHI-10 score was significantly higher in the study group compared to the control group (2.21 ± 4.05 vs 0.95 ± 2.60, $P = 0.025$). However, no significant difference in the prevalence of VHI-10 score above 11 was found between the two groups (four patients vs one patient, $P > 0.05$; Table 2).

Likert scale for vocal fatigue and hoarseness

The mean Likert scale for hoarseness was significantly higher in the study group compared to the control group (1.20 ± 1.92 vs 0.47 ± 1.24, $P = 0.002$). However, there was no significant difference in the mean Likert scale for vocal fatigue in those on statin versus those not on statin (0.82 ± 1.86 vs 0.62 ± 1.73, $P > 0.05$; Table 2).

EAT-10

The mean EAT-10 score was significantly higher in patients on statin therapy versus those not on statin therapy (2.40 ± 3.77 vs 0.92 ± 2.24, $P = 0.001$). Although the prevalence of EAT-10 score ≥3 was higher in the study group as compared to the control group, it did not reach statistical significance (22 patients vs 12 patients, $P > 0.05$; Table 2).

DISCUSSION

Statin-induced myopathy is a commonly encountered adverse event that can be divided into four different subsets, namely myalgia or mild hyperCKemia (creatinine kinase level <5 times the upper limit of normal), self-limited toxic statin myopathy, myositis that has recently been described as immune-mediated necrotizing myopathy with anti-HMGCR antibodies, and rhabdomyolysis with evidence of severe muscle necrosis. Patients present clinically with an

TABLE 2.
Prevalence of Dysphonia and Dysphagia Symptoms Using VHI-10, Likert Scale, and EAT-10

	Statin Group ($N = 75$)	Control ($N = 85$)	*P* Value
VHI-10			
Mean ± SD	2.21 ± 4.05	0.95 ± 2.60	0.025
Likert scale			
Vocal fatigue	0.82 ± 1.86	0.62 ± 1.73	0.111
Hoarseness	1.20 ± 1.92	0.47 ± 1.24	0.002
EAT-10			
Mean ± SD	2.40 ± 3.77	0.92 ± 2.24	0.001

array of vague symptoms that include muscle fatigue, pain, weakness, and tenderness. These symptoms usually affect the proximal extremities in a symmetrical fashion resulting in cessation of therapy in one out of five patients.[15,16]

Although statin-induced myopathy can theoretically involve any muscle, it has rarely been described in relation to the laryngopharyngeal complex. Hamdan et al, in their prospective study on the severity and frequency of vocal tract symptoms in patients on statins versus those not on statins, found no statistically significant difference between the two groups. The study was conducted using the vocal tract discomfort scale on a total of 73 patients (44 on statins and 29 not on statins).[17] Given the limitation of that study, namely the small number of cases, the authors of this study were intrigued to further investigate the prevalence of phonatory and swallowing symptoms in a larger group of patients on statins using self-reported questionnaires, namely the VHI-10 and EAT-10. The hypothesis set forth was that there is a significant difference between the study group and controls. Indeed, based on the result of this investigation, the mean scores of VHI-10, EAT-10, and Likert scale for hoarseness were significantly higher in the study group compared to the control group. However, it is important to note that the results of this investigation do not provide information on the nature of dysphonia and dysphagia, nor on the origin of these symptoms. The change in voice quality can be secondary to impairment in breathing and or reduced vocal fold vibration, both of which were not ruled out in this study. Similarly, the origin of dysphagia be it oropharyngeal hypopharyngeal or esophageal cannot be concluded from the current data.

The results of this investigation are not surprising given that the laryngopharyngeal complex is a musculoskeletal structure similar to other musculoskeletal structures in the body. Several mechanisms have been implicated in statin-induced myopathy. One suggested mechanism is inhibition of HMG-CoAR, which results in a decrease in geranylgeranyl prenylation promoting apoptosis and proteolysis. Another suggested mechanism is impairment in mitochondrial function and lipid oxidation by inhibiting coenzyme Q10 leading to apoptosis. Also, statins can cause membrane lysis by altering membrane cholesterol, impair muscle protein synthesis, and trigger an autoimmune process within muscle cells.[18]

On the other hand, the lack of significant difference in the mean Likert scale for vocal fatigue between the two groups can be attributed to two main factors. First is the difference in the histologic features between intrinsic laryngopharyngeal muscle fibers and extremity muscle fibers. Each muscle in the body has a specific muscle fiber type composition that reflects its function and is broadly classified into two phenotypes, slow contracting type I fibers and fast contracting type II fibers, each of which expresses a different myosin heavy chain isoform that regulates contraction speed.[19] Type II muscle fibers are further divided into types IIA and IIB fibers. The former produces muscular power for a short duration of time and is considered more resistant to fatigue compared to type IIB. Unlike muscles of the extremities, the laryngeal muscles are composed of higher percentage of type 1 fibers that are slow twitch and highly resistant to fatigue.[20] Sataloff et al corroborated the aforementioned by describing a distinguished histologic architecture of fibers arrangement in the thyroarytenoid muscle that further explains the fatigue-resistant characteristic of this muscle.[21] A second possible explanation for the lack of significant difference in the mean Likert scale between the two groups is the mean duration of statin therapy at the time of investigation. This latter was 74.92 months in average, whereas the average time for muscle related symptoms to occur has been reported to be around 6.3 months of statin therapy.[22]

This study is the second to investigate the association between the intake of statins and laryngopharyngeal symptoms, namely dysphonia and dysphagia. Despite the presence of such an association evidenced by the significant difference in the mean score of VHI-10 and EAT-10 scores between the study group and controls, the cause effect relationship cannot be asserted. The findings of this study can be secondary to comorbid diseases not accounted for in the study group or the result of other drug-induced side effects.

This study has many limitations. One is lack of laryngeal examination or functional endoscopic evaluation of swallowing to rule out laryngeal functional or organic pathologies, the presence of which may be responsible for the higher mean score of VHI-10 and EAT-10. Second is the lack of objective testing of laryngeal and pharyngeal muscle function and the lack of objective phonatory measures such as acoustic or aerodynamic analysis, which may help in detecting subtle vocal changes. Another limitation is the relatively small number of subjects enrolled and the lack of information on the vocal tasks performed by the participants prior to their enrollment in the study. Information on the phonatory behavior and extent of vocal loading is important in the interpretation of symptoms related to statin-induced myopathy.[15]

CONCLUSION

This investigation revealed a statistically significant difference in the prevalence of laryngopharyngeal symptoms in patients on statin therapy versus a control group. Nevertheless, it is important to note that the mean score values of both VHI-10 and EAT-10 did not reach abnormal levels. Future studies using comprehensive voice and swallowing evaluation in addition to electromyographic analysis of laryngopharyngeal muscles will further delineate the effect of statin-induced myopathy on the laryngopharyngeal structures.

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