

## Research Article

# Are Chronic Pain Syndromes the Reason for Statin-Associated Muscle Symptoms?

Sheinin R<sup>1,2#</sup>, Nogueira AR<sup>1#</sup>, Bragazzi NL<sup>3</sup>, Watad A<sup>1,2</sup>, Tiosano S<sup>1,2</sup>, Gonen T<sup>1,2</sup>, Yavne Y<sup>1,2</sup>, Sharif K<sup>1,2</sup>, Kameri Y<sup>2,4</sup>, Amital D<sup>2,5</sup>, Amital H<sup>1,2#</sup> and Cohen H<sup>2,4#\*</sup>

<sup>1</sup>Department of Medicine 'B' & The Zabudowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-HaShomer, Ramat-Gan, Israel

<sup>2</sup>Sackler Faculty of Medicine, Tel-Aviv University, Israel

<sup>3</sup>Postgraduate School of Public Health, Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy. Laboratory for Industrial and Applied Mathematics (LIAM), Department of Mathematics and Statistics, York University, Toronto, ON, Canada

<sup>4</sup>The Bert W. Strassburger Lipid Center, Sheba Medical Center, Tel-HaShomer, Ramat-Gan, Israel

<sup>5</sup>Division of Psychiatry, Barzilai Medical Center, Ashkelon, Israel

#Contributed Equally to this Work

\*Corresponding author: Cohen H, The Bert W. Strassburger Lipid Center, Sheba Medical Center, Tel-HaShomer, 5265601 Israel

Received: February 08, 2022; Accepted: April 15, 2022; Published: April 22, 2022

## Abstract

**Background:** Statin induced myalgia is defined as muscle pain without elevation of serum creatine phosphokinase levels, and is a well-known complaint among statin users. Chronic pain syndromes affect a high percentage of the population; and it may be possible that these pain syndromes confound the reports of statin induced myalgia. We sought to compare the occurrence of chronic pain among patients on statin therapy who developed myalgia with those who did not.

**Methods:** This study included 112 statin-treated patients, followed up at the clinic of the Lipid Center in Sheba Medical Center. Fifty-six of the subjects had a diagnosis of statin associated muscle symptoms (SAMS) and 56 did not. Verified questionnaires were used to assess the diagnoses of fibromyalgia, pain intensity, functional impairment, anxiety and depression in the study population.

**Results:** Patients with statin myalgia were more likely to fulfil the diagnostic criteria for fibromyalgia than patients without statin myalgia (11 (19.6%) vs. zero, respectively). Patients in the SAMS group also exhibited higher levels of anxiety and depression in comparison with the control group. Female sex, higher scores on the Brief Pain Inventory pain intensity scale, and a Hamilton rating scale level indicative of an anxiety disorder were found to be significant predictors for fibromyalgia in patients suffering from statin myalgia.

**Conclusion:** A significant percentage of patients, diagnosed with statin myalgia actually fulfilled the diagnostic criteria for fibromyalgia, depression or anxiety disorder. Detection of these patients and treatment of their primary pain disorder or psychiatric illness has the potential to prevent unnecessary cessation of effective statin therapy.

**Keywords:** Statin; Myalgia; Pain; Adherence; Fibromyalgia; Anxiety; Depression

## Abbreviations

CPK: Creatine Phosphokinase; CK: Creatine Kinase; SAMS: Statin Associated Muscle Symptoms; ACR: American College of Rheumatology; WPI: Wide-Spread Index; SS: Symptom Severity; BPI: Brief Pain Inventory; MINI: Mini-International Neuropsychiatric Interview; BMI: Body Mass Index; SD: Standard Deviation; OR: Odds Ratio; ASCVD: Atherosclerotic Cardiovascular Disease.

## Introduction

Statins (3-Hydroxy-3-methyl-glutaryl-CoA reductase inhibitors) are a highly effective medications class, currently used for treating hypercholesterolemia and for primary and secondary prevention of atherosclerotic cardiovascular disease. Statins are commonly prescribed in clinical practice, and are usually well-tolerated [1]. However, overall statin intolerance is observed in 10-15% of patients treated with statins, limiting treatment adherence and affecting potential outcomes [2,3]. Most adverse effects associated with statin therapy is muscle-related [2], defined as SAMS - Statin Associated Muscle Symptoms. The most common symptom of SAMS is myalgia, described as unexplained muscle discomfort, including muscle aches or pains, in the absence of creatine kinase (CK) elevation [4]. Other

types of SAMS include myopathy, myositis, and muscle injury-rhabdomyolysis; all are much rarer muscle disorders than myalgia [3,5]. The incidence of myalgia complaints as an adverse effect of statins greatly varies between controlled clinical trials (1-5%) and observational cohorts (11-29%) [6].

In several blinded clinical trials, comparing statin therapy with placebo, there were no significant differences in the fraction of patients with myalgia following both treatments. In other studies, a significant difference was reported, yet high rates of myalgia were also observed in the placebo groups [7-11]. These studies demonstrated the significant role of the nocebo effect, suggesting that the underlying mechanism behind statin myalgia may include a psychosomatic component. In a cross-sectional study of 1,924 subjects, Korhonen et al., [12] reported that statin non-adherence rate was increased by 33% in patients with somatic symptoms of anxiety (rapid pulse, sweating, flushing, etc.) on a daily or weekly basis, in comparison with patients without these symptoms. In a systematic review and meta-analysis assessing factors associated with non-adherence to statin therapy, in individuals older than 65 years, it was found that depression was significantly related with increased rates of nonadherence [13]. The symptoms of muscle pain in SAMS, share common features with the symptoms

of fibromyalgia. Fibromyalgia is a chronic pain syndrome, which more commonly affects women (ratio of 5:1). The dominant feature of fibromyalgia is diffuse musculoskeletal pain, and in the past two decades, the definition of fibromyalgia has broadened to additionally include fatigue, cognitive impairment and sleep disorders [14]. The analogous characteristics of both statin myalgia and fibromyalgia, expressed as typical muscle pain led us to hypothesize that a certain portion of patients presenting with SAMS are actually suffering from undiagnosed fibromyalgia. To the best of our knowledge, this is the first study to examine the presence of fibromyalgia or other affective disorders among patients suffering from SAMS.

## Materials and Methods

### Study population

The study population was comprised of patients with a diagnosis of hypercholesterolemia, from the outpatient lipid clinic at Sheba Medical Center, Tel-HaShomer in Israel. Inclusion criteria included past or current statin therapy, age over 18 and under 65 years, and normal thyroid function. Exclusion criteria included women who were pregnant or breastfeeding, previous or current diagnosis of malignancy (excluding cutaneous basal cell carcinoma), substance abuse (current or past), major psychiatric illness, diagnosis of rheumatic or inflammatory conditions, previously documented fibromyalgia, or any underlying disease-causing significant disability.

### Study design

This study was designed as a cross-sectional study. Subjects were divided into two groups: patients with a diagnosis of SAM and patients without myalgia under statin therapy (i.e. the control group). Statin associated myalgia, was defined as muscle pain occurring while a subject was on statin therapy that resulted in the discontinuation of treatment or in a change of the therapy regimen to another statin. The patients were recruited between September 1<sup>st</sup> 2016 and September 1<sup>st</sup> 2018. The local ethical committee of the Sheba Medical Center, Tel-HaShomer, Israel, approved the study. Informed consent was obtained from each patient.

### Clinical assessment

Each subject enrolled in the study, underwent an initial assessment, which included the collection of demographic and medical data, past medical history (including any current or past psychiatric disorder), smoking status, and alcohol or substance abuse. Additionally, information regarding history of statin therapy was obtained. The type of hypercholesterolemia (familial or primary), type of prevention provided by therapy (primary or secondary), age at diagnosis, age in which statin therapy was initiated, number of previously statins tried as well as statin dose and type. Duration of treatment prior to the onset of myalgia was not always available as continuous, accurate values, and, as such, was categorized in days, weeks, months or years. CPK and vitamin D serum levels were also obtained for all subjects at the time of enrolment in the study.

Each patient completed a well-validated questionnaire, which included a functional and mental evaluation:

- Diagnosis of fibromyalgia according to the 2010 American College of Rheumatology (ACR) [14]. These classification criteria included calculations of the widespread index (WPI) and the

symptom severity (SS) scores.

- Pain assessment using the Brief Pain Inventory (BPI) questionnaire [15].
- Evaluation of depression and anxiety was done by using the Hamilton rating scale for Depression and Anxiety [16,17].
- Severity of depression was categorized as following: 10-13 mild; 14-17 mild to moderate; >17 moderate to severe; severity of anxiety was categorized as a score of 17 or less - mild anxiety severity, 18 to 24 - mild to moderate anxiety, 25 to 30 - moderate to severe anxiety.
- Evaluation of patients' daily disability using the Sheehan questionnaire [18].
- Evaluation of the existence of psychiatric disorders through the implementation of the Mini-International Neuropsychiatric Interview (MINI) abbreviated questionnaire [19].

### Statistical analysis

Prior to proceeding with data manipulation, figures were visually inspected for potential outliers. Normality of data distribution was assessed by the D'Agostino-Pearson omnibus test. Unordered chi-squared or exact Fisher Test was used for categorical variables. If these were ordered (i.e., ordinal parameters, such as vitamin D status, statin dose, anxiety and depression levels), the Cochran-Armitage test for trend (known also as the ordered chi-squared test for trend) was applied, besides the classical (and less powerful) unordered test. More specifically, this test enables to capture the potential effects of the ordering of the n categories of a given ordinal variable. For continuous parameters, Student's t-test and analysis of variance (ANOVA) or their non-parametrical versions (Wilcoxon rank-sum test, also known as Mann-Whitney U test, and Kruskal-Wallis) were carried out at the univariate analysis in order to reveal statistical differences between statin users with and without myalgia and fibromyalgia cases, respectively. The Bonferroni test was used as a post-hoc test for adjusting for multiple pairwise comparisons. Multivariable logistic regression analysis was conducted to analyze the predictors of myalgia among statin users. In more detail, deferent models were run, with various predictors and the best model was chosen based on the findings of the univariate analysis, the Hosmer-Lemeshow test and the highest predictive power in terms of the value of the "area under the curve" (AUC) and Cox and Snell's R-squared. All statistical analyses were carried out using the commercial software "Statistical Package for the Social Sciences" (SPSS v24, IBM, USA), while graphs were generated by the MedCalc Statistical Software version 17.9.7 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2017). Figures with p-values of less than 0.05 were considered statistically significant.

## Results

### Study population baseline characteristics

The study population included 112 patients (56 subjects with SAMS and 56 controls without myalgia). The mean age of the study population was 51.9±11.8 years; 60.7% of the subjects were male. The mean body mass index (BMI) was 26.4±4.1 kg/m<sup>2</sup>. Thirty-seven subjects (33.0%) consumed alcohol and 17 (15.2%) were

**Table 1:** Study population baseline characteristics.

Variable	Value
Age (mean ± SD)	51.89±11.81
Gender	
Male	68 (60.7%)
Female	44 (39.3%)
BMI (mean ± SD)	26.36±4.11
Alcohol consumption	37 (33.0%)
Current smoking status	17 (15.2%)
Engagement in physical activity	81 (72.3%)
Times per week (mean)	2.27±1.87
Intensity of physical activity	
Light	22 (19.6%)
Light-medium	12 (10.7%)
Medium	37 (33.0%)
Medium-hard	9 (8.0%)
strenuous	4 (3.6%)
Type of physical activity	
Aerobic	67 (59.8%)
Anaerobic	4 (3.6%)
Both	13 (11.6%)
Diagnosis with a psychiatric disorder (current/past)	10 (8.9%)
Vitamin D-mean±SD serum concentrations (ng/ml)	33.74±15.40
Deficient	1 (0.9%)
Insufficient	12 (10.7%)
Regular use of a vitamin D supplement	43 (38.4%)
CPK (IU/L) – mean serum levels	260.90±637.07
Therapy purpose	
Primary prevention	78 (69.6%)
Secondary prevention	34 (30.4%)
Duration of treatment (years, mean)	9.9±7.4
Duration of dyslipidemia diagnosis (years, mean±SD)	12.2±8.4
Current statin used	88 (78.6%)
Rosuvastatin	41 (46.6%)
Atorvastatin	39 (44.3%)
Simvastatin	3 (3.4%)
Pravastatin	5 (5.7%)
Current dose of statin	
Very low	11 (12.5%)
Low	41 (46.6%)
Medium	17 (19.3%)
High	19 (21.6%)
Current ezetimibe use	41 (36.6%)
Concomitant treatment with statins and ezetimibe	33 (29.5%)
Number of treatment lines attempted	2.98±1.50
Scores on questionnaires (mean±SD)	

WPI	1.86±2.83
SS2a	1.81±1.85
SS2b	1.16±0.61
BPI pain intensity	4.28±7.61
BPI pain interference	5.50±12.11
Hamilton Depression scale	5.18±4.68
Normal	87 (77.7%)
Mild	15 (13.4%)
Moderate	7 (6.3%)
Severe	3 (2.7%)
Hamilton Anxiety scale	7.60±5.99
Normal	105 (93.8%)
Mild-to-moderate	3 (2.7%)
Moderate-to-severe	4 (3.6%)
Sheehan disability scale score (mean±SD)	4.93±7.26
MINI score compatible with a diagnosis of:	
A short depressive state	12 (10.7%)
A short manic state	5 (4.5%)
Short panic attacks	19 (17.0%)
Short social phobia	3 (2.7%)

BMI: Body Mass Index; CPK: Creatine Phosphokinase; WPI: Wide Spread Pain Index; SS: Symptom Severity; MINI: Mini-International Neuropsychiatric Interview.

current smokers. Most of the patients had co-morbidities (103 patients, 92.0%): 10 (8.9%) subjects had an established diagnosis of psychiatric disorders and 11 (9.8%) reported having a familial history of psychiatric diseases. Vitamin D deficiency (25 hydroxy-vitamin D <10ng/ml) was found in one subject (0.9%), whereas twelve patients (10.7%) had vitamin D insufficiency (levels of 10ng/ml <25 hydroxy-vitamin D <30ng/ml). Forty-three subjects (38.4%) were using vitamin D supplementation, and five (4.5%) had a diagnosis of osteoporosis.

Seventy-eight subjects (69.6%) were being treated with statins as primary prevention for atherosclerotic cardiovascular disease (ASCVD). The most prescribed statins were rosuvastatin and atorvastatin (46.6% and 44.3%, respectively). Prior to enrollment in the study, patients had been treated on average with statins for 9.9±7.4 years, while the mean duration of hypercholesterolemia was 12.2±8.4 years. The mean number of different statins previously used by the subjects was 3.0±1.5. Most patients' depression scores were within the defined normal range (77.7%), whilst 13.4%, 6.3% and 2.7% had scores compatible with mild, moderate and severe depression, respectively. The mean Hamilton depression score was 5.2±4.7, whilst the mean Hamilton anxiety score was 7.6±6.0 (Table 1).

### Comparison between statin-treated patients with and without myalgia

The univariate analysis revealed that the control group and that statin myalgia group differed from one another statistically when assessed for several clinical variates (Table 2 and 3). Duration of statin therapy was significantly shorter in the control group compared with the myalgia group (8.3±7.4 and 11.5±7.1 years (mean±SD)

**Table 2:** Univariate analysis of statin myalgia subjects versus controls: socio-demographic parameters.

Variable	Controls	Myalgia cases	Statistical significance
Age (mean±SD)	49.71±12.91	54.07±10.25	0.075
Gender			0.033
Male	40 (71.4%)	28 (50.0%)	
Female	16 (28.6%)	28 (50.0%)	
BMI (mean±SD)	25.66±3.29	27.06±4.71	0.07
Marital status (married)	40 (71.4%)	40 (71.4%)	1
Educational level			0.437
High school	19 (33.9%)	24 (42.9%)	
University	37 (66.1%)	32 (57.1%)	
Employed	47 (83.9%)	43 (76.8%)	0.476
Alcohol consumption	22 (39.3%)	15 (26.8%)	0.228
Current smoking	9 (16.1%)	8 (14.3%)	1
Engagement in physical activity	40 (71.4%)	41 (73.2%)	1
Times per week (mean±SD)	2.10±1.66	2.44±2.06	0.585
Intensity of physical activity			0.184
light	12 (21.4%)	10 (17.9%)	
light-medium	7 (12.5%)	5 (8.9%)	
Medium	17 (30.4%)	20 (35.7%)	
Medium-hard	2 (3.6%)	7 (12.5%)	
Strenuous	4 (7.1%)	0 (0.0%)	
Type of physical activity			0.779
Aerobic	33 (58.9%)	34 (60.7%)	
Anaerobic	3 (5.4%)	1 (1.8%)	
Both	6 (10.7%)	7 (12.5%)	

BMI: Body Mass Index.

respectively,  $p=0.002$ ), and the percentage of subjects in the myalgia group being treated with statins at the time of enrolment compared with the control group was significantly lower (58.9% and 98.2% respectively,  $p < 0.001$ ). Statin dose also differed significantly between the control and the myalgia group: patients with myalgia were being treated with much lower doses of statins ( $p=0.004$ ). Patients in the myalgia group were also found to have attempted a significantly higher number of treatment lines, compared with the control group (3.79±1.33 and 2.18±1.21 (mean±SD), respectively,  $p < 0.0001$ ).

The myalgia group had significantly higher scores on all of the following assessment scales and scores for depression, anxiety, and pain intensity ( $p < 0.0001$ ): WPI score, SS score, BPI pain intensity score, BPI pain interference score, Hamilton depression scale, and the Hamilton anxiety scale.

The multivariable logistic regression analysis (Table 4) found that female sex (OR=2.34 [95% CI 1.00-5.46],  $p=0.050$ ) and a higher Hamilton anxiety score (OR=1.16 [95% CI 1.06-1.27],  $p=0.001$ ) were both independent predictors of myalgia in statin users.

Among the statin myalgia group, 11 of 56 subjects (19.6%) fulfilled the 2010 ACR criteria for fibromyalgia (Figure 1). With respect to the entire study population, the subjects with myalgia,

**Table 3:** Univariate analysis of myalgia cases versus controls: clinical parameters.

Variable	Controls	Myalgia cases	Statistical significance
Presence of any comorbidity	49 (87.5%)	54 (96.4%)	0.162
Diabetes Mellitus	6 (10.7%)	7 (12.5%)	1
Psychiatric disorders	6 (10.7%)	4 (7.1%)	0.742
Family history of psychiatric disorders	7 (12.5%)	4 (7.1%)	0.527
Serum vitamin D (ng/ml) (mean ± SD)	32.78±14.66	34.64±16.19	0.62
Vitamin D status			0.511 (1.000 for trend)
Deficient	1 (1.8%)	0 (0.0%)	
Insufficient	5 (8.9%)	7 (12.5%)	
Sufficient	50 (89.3%)	49 (87.5%)	
Use of a vitamin D supplement	17 (30.4%)	26 (46.4%)	0.12
Osteoporosis	0 (0.0%)	5 (8.9%)	0.057
Serum CPK (IU/L) - mean±SD	213.16±554.44	310.63±715.67	0.066
Therapy purpose			0.538
Primary prevention	41 (73.2%)	37 (66.1%)	
Secondary prevention	15 (26.8%)	19 (33.9%)	
Treatment duration (years)	8.33±7.37	11.54±7.09	0.002
Duration of treatment prior to onset of myalgia	-	-	-
Days		18 (32.1%)	
Weeks		10 (17.9%)	
Months		17 (30.4%)	
Years		11 (19.6%)	
Reported myalgia under low statin doses	-	31 (55.4%)	-
Disease duration (years, mean±SD)	11.05±8.41	13.34±8.39	0.07
Current use of statins	55 (98.2%)	33 (58.9%)	0
Type of statin			0.021 (0.004 for trend)
Rosuvastatin	22 (40.0%)	19 (57.6%)	
Atorvastatin	27 (49.1%)	12 (36.4%)	
Simvastatin	3 (5.5%)	0 (0.0%)	
Pravastatin	3 (5.5%)	2 (6.1%)	
Statin dose			0.021 (0.004 for trend)
Very low	3 (5.5%)	8 (24.2%)	
Low	24 (43.6%)	17 (51.5%)	
Medium	13 (23.6%)	4 (12.1%)	
High	15 (27.3%)	4 (12.1%)	
Use of ezetimibe	16 (28.6%)	25 (44.6%)	0.116
Concomitant treatment with statins and ezetimibe	16 (28.6%)	17 (30.4%)	1
Other concomitant medications	37 (66.1%)	46 (82.1%)	0.075
Number of previous statin treatment lines attempted	2.18±1.21	3.79±1.33	<0.0001
Number of treatment lines attempted prior to myalgia onset	-	3.32±1.54	-
Scores on questionnaires administered (mean±SD)			
WPI	0.43±1.02	3.29±3.31	<0.0001



SS2a	1.20±1.37	2.43±2.06	<0.0001
SS2b	0.98±0.59	1.34±0.58	<0.0001
BPI pain intensity scale	0.41±1.44	8.14±9.18	<0.0001
BPI pain interference scale	1.18±5.43	9.82±15.11	<0.0001
Hamilton Depression scale	3.89±4.20	6.46±4.82	<0.0001
Hamilton Depression cut-off			
Normal	47 (83.9%)	40 (71.4%)	0.426 (0.112 for trend)
Mild	6 (10.7%)	9 (16.1%)	
Moderate	2 (3.6%)	5 (8.9%)	
Severe	1 (1.8%)	2 (3.6%)	
Hamilton Anxiety scale score (mean±SD)	5.48±4.94	9.71±6.23	<0.0001
Hamilton Anxiety cut-off			
Normal	55 (98.2%)	50 (89.3%)	0.120 (0.098 for trend)
Mild-to-moderate	0 (0.0%)	3 (5.4%)	
Moderate-to-severe	1 (1.8%)	3 (5.4%)	
Sheehan disability scale score (mean±SD)	3.98±6.67	5.88±7.74	0.253
nMINI score compatible with a diagnosis of:			
A short depressive state	5 (8.9%)	7 (12.5%)	0.761
A short manic state	2 (3.6%)	3 (5.4%)	1
Short panic attacks	10 (17.9%)	9 (16.1%)	1
Short social phobia	0 (0.0%)	3 (5.4%)	0.243
Fulfillment of FM 2010 ACR criteria	0 (0.0%)	11 (19.6%)	0.001

CPK: Creatine Phosphokinase; WPI: Wide Spread Pain Index; SS: Symptom Severity; MINI: Mini-International Neuropsychiatric Interview; FM: Fibromyalgia; Vitamin D Levels: Sufficient >30ng/ml; Insufficient <30ng/ml; deficient <10ng/ml.

scored higher in the BPI pain intensity scale ( $p < 0.0001$ ), BPI pain interference scale ( $p < 0.0001$ ), Hamilton depression scale ( $p = 0.001$ ), and Hamilton anxiety scale ( $p < 0.0001$ ) scores. According to a multivariable regression analysis, increased BPI score (OR=1.47 [95% CI 1.21-1.80],  $p = 0.0000$ ), increased Hamilton anxiety score (OR=1.22 [95% CI 1.05-1.41],  $p = 0.011$ ) and female sex (OR=8.01 [95% CI 1.15-55.94],  $p = 0.036$ ) were all significant predictors of coexistent fibromyalgia (Table 4).

### Fibromyalgia and physical activity

Physical activity at any level was reported by 81 subjects (72.3% of the subjects included in the study). On average, recruited individuals performed physical activity 2.3±1.9 times per week. Intensity of physical activity was easy in 22 cases (19.6%), whereas 12 (10.7%) and 37 subjects (33.0%) reported easy-to-medium and medium intensity, respectively. Medium-to-hard and hard physical activity was practiced by nine (8.0%) and four individuals (3.6%), respectively. The myalgia group as well as the subgroup of subjects who fulfilled the criteria for fibromyalgia did not differ in terms of physical activity performance, intensity or type. However, the two groups diverged regarding the regularity of physical activity ( $p = 0.0053$ ). The myalgia and fibromyalgia subgroups did not differ in terms of serum CPK values measured ( $p = 0.890$ ).

## Discussion

This study is one of the first attempts to evaluate the association

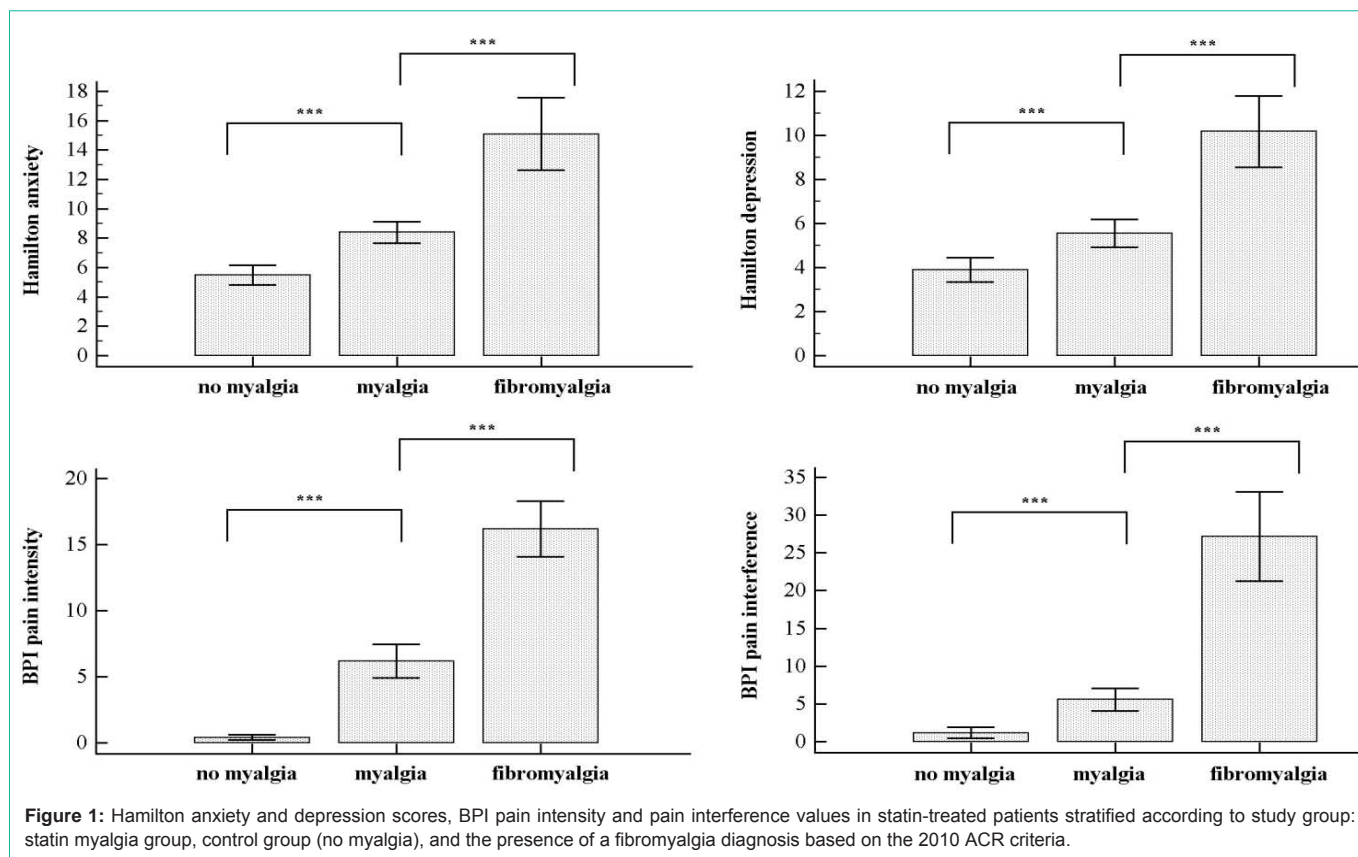
between fibromyalgia, mood disorders and statin myalgia. Our results demonstrate that about a fifth of suspected SAMS patients, were actually found to have concomitant fibromyalgia. In addition, patients in the myalgia group exhibited various characteristics of anxiety and depression compared to the control group. Our results can partially explain the differences between the prevalence of statin intolerance according to clinical reports and those observed by randomized controlled trials [5]. Out of the patients' characteristics and evaluations performed in the study, female sex, high scores of the BPI pain intensity and the Hamilton anxiety scale, were all found to be significant predictors for fibromyalgia in patients suffering from statin myalgia.

Other publications examined potential predictors for SAMS; the authors of the "Prediction of Muscular Risk in Observational conditions (PRIMO)" study from 2006 reported that depression (current or past diagnosis) did not have any impact on mild to moderate muscular symptoms with high-dosage statin therapy. However, the same study found that treatment with antidepressants was associated with a decreased risk of muscular symptoms [20]. Therefore, it is possible that appropriate treatment with antidepressant can diminish the incidence of SAMS in patients with depression.

Undeniably, the association between statins and depression is quite complex. Cholesterol has an important role in the serotonergic system, thus, theoretically, statins may lead to depression in a mechanism that involves a decrease in cholesterol levels [21]. Nevertheless, in a meta-analysis by Parsaik et al., [22] statin use was associated with a lower risk for depression. This observation may indirectly support the pleomorphic effects of statins, of anti-inflammatory and anti-oxidative effects on autoimmune and cardiovascular disorders [23-26]. Several recent reports, failed to support a possible link between statin use and depression suggesting that the reported associations were due to confounding factors [27,28].

The occurrence of myalgia as an adverse effect of statin therapy varies in different studies. These differences were partially explained by different inclusion and exclusion criteria and to the absence of a specific biomarker for myalgia turning its definition inconsistent [6,7].

Wood et al. [29] presented subjects, who reported statin related muscle side effects, necessitating statin withdrawal. By re-challenging them with either a statin, or a placebo, 90% of the symptom burden associated with statin was similarly associated with placebo meaning that in the majority of these individuals; their symptoms reappeared regardless if a placebo or a statin were given. Furthermore, half of study participants were able to re-start successfully statins [29]. Data are lacking, regarding the association between anxiety and statin use. It has been proposed that statins may have an anxiolytic effect as they act as a NMDA (N-methyl-D-aspartate) [30]. In addition, it has been demonstrated, that a higher awareness of medication side effects leads to an increase in intolerance and non-adherence [31]. This effect may be more prominent in patients with preliminary anxiety symptoms and may partly explain the association between SAMS and anxiety found in our study. There is also scarce data regarding the association between statins and fibromyalgia. Mascitelli et al. [32] stated that statin therapy might adversely affect muscle strength and



**Table 4:** Predictors of myalgia in statins users at the multivariable logistic regression analysis.

Variable	B	Standard error	Wald	Sig.	OR	95% CI (OR)	
						Lower bound	Upper bound
Hamilton anxiety scale score	0.15	0.04	11.13	0.001	1.16	1.06	1.27
Sex (female)	0.85	0.43	3.85	0.05	2.34	1	5.46
Constant	-3.02	1.06	8.17	0.004			

therefore interfere with the implementation of physical activity in patients with suspected fibromyalgia, thus leading to over diagnosis of fibromyalgia.

A well-known risk factor for SAMS is female sex [33] and indeed, in our study, the percentage of women in the SAMS group was higher in comparison with the control group. No differences were observed between the groups in terms of age, ethnic origin, and country of birth, marital status, education, occupational status, and rates of cigarette smoking. While intense physical activity, vitamin D deficiency, diabetes mellitus, alcohol consumption, increased serum CPK levels, and low BMI, are all known risk factors for SAMS [34,35], no significant differences between these variables were measured in our study, comparing the control group to the myalgia group. These findings suggest that the aetiology of SAMS is certainly diverse and multi-factorial.

As for the timing of symptoms, in the current study, 81.4% of the myalgia group reported that muscle pain began within a few months of initiating statin therapy. This is in concordance with the current literature in which approximately 90% of patients who develop SAMS

experience symptoms do so within the first six months of treatment and 75% of patients do so within the first 10-12 weeks [2].

The main limitation of our study is the potential selection bias as the statin-treated population represents the patients from a large tertiary facility, the Sheba Medical Center, Israel. Therefore, the participants of our study may fully not reflect the composition of patients as seen in primary care settings. Additional drawbacks derive from the relatively small number of patients and the variable definitions of SAMS in the literature [5]. In the current study, we used the definition of SAMS for patients with muscle pain under statin therapy that discontinued statins due to these symptom, nonetheless other studies had differently defined SAMS.

## Conclusion

The results of this study demonstrate that a significant portion of patients who discontinue statin therapy due to myalgia, have actually an underlying diagnosis either fibromyalgia or a concomitant mood disorder. We suggest that prompt detection of these patients and administration of proper treatment may prevent untimely statin cessation, increased cardiovascular morbidity and mortality.

## Conflict of Interest and Financial Disclosures

The authors declare that there were no financial or other potential conflict of interests. Any third party did not fund this study; and the research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

## References

- Schwartz GG, Fayyad R, Szarek M, DeMicco D, Olsson AG. Early, intensive statin treatment reduces 'hard' cardiovascular outcomes after acute coronary syndrome. *Eur J Prev Cardiol.* 2017; 24: 1294-1296.
- Banach M, Rizzo M, Toth PP, Farnier M, Davidson MH, Al-Rasadi K, et al. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. *Arch Med Sci.* 2015; 11: 1-23.
- Toth PP, Patti AM, Giglio RV, Nikolic D, Castellino G, Rizzo M, et al. Management of Statin Intolerance in 2018: Still More Questions Than Answers. *Am J Cardiovasc Drugs.* 2018; 18: 157-173.
- Cho L, Rocco M, Colquhoun D, Sullivan D, Rosenson RS, Dent R, et al. Clinical Profile of Statin Intolerance in the Phase 3 GAUSS-2 Study. *Cardiovasc Drugs Ther.* 2016; 30: 297-304.
- Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert Panel null. An assessment by the Statin Muscle Safety Task Force: 2014 update. *J Clin Lipidol.* 2014; 8: S58-71.
- Ganga HV, Slim HB, Thompson PD. A systematic review of statin-induced muscle problems in clinical trials. *Am Heart J.* 2014; 168: 6-15.
- Davis JW, Weller SC. Intensity of statin therapy and muscle symptoms: a network meta-analysis of 153000 patients. *BMJ Open.* 2021; 11: e043714.
- Taylor BA, Thompson PD. Muscle-related side-effects of statins: from mechanisms to evidence-based solutions. *Curr Opin Lipidol.* 2015; 26: 221-227.
- Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve FJ, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol.* 2015; 9: 758-769.
- Nissen SE, Stroes E, Dent-Acosta RE, Rosenson RS, Lehman SJ, Sattar N, et al. Efficacy and Tolerability of Evolocumab vs. Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial. *JAMA.* 2016; 315: 1580-1590.
- Parker BA, Capizzi JA, Grimaldi AS, Clarkson PM, Cole SM, Keadle J, et al. Effect of statins on skeletal muscle function. *Circulation.* 2013; 127: 96-103.
- Korhonen MJ, Pentti J, Hartikainen J, Kivimäki M, Vahtera J. Somatic symptoms of anxiety and nonadherence to statin therapy. *Int J Cardiol.* 2016; 214: 493-499.
- Ofori-Asenso R, Jakhu A, Curtis AJ, Zomer E, Gambhir M, Jaana Korhonen M, et al. A Systematic Review and Meta-analysis of the Factors Associated with Nonadherence and Discontinuation of Statins Among People Aged ≥65 Years. *J Gerontol A Biol Sci Med Sci.* 2018; 73: 798-805.
- Wolfe F, Clauw DJ, Fitzcharles M-A, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken).* 2010; 62: 600-610.
- Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap.* 1994; 23: 129-138.
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960; 23: 56-62.
- Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol.* 1959; 32: 50-55.
- Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. *Int Clin Psychopharmacol.* 1996; 11: 89-95.
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* 1998; 59: 22-33; quiz 34-57.
- Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. *Cardiovasc Drugs Ther.* 2005; 19: 403-414.
- You H, Lu W, Zhao S, Hu Z, Zhang J. The relationship between statins and depression: a review of the literature. *Expert Opin Pharmacother.* 2013; 14: 1467-1476.
- Parsaik AK, Singh B, Murad MH, Singh K, Mascarenhas SS, Williams MD, et al. Statins use and risk of depression: a systematic review and meta-analysis. *J Affect Disord.* 2014; 160: 62-67.
- Chodick G, Amital H, Shalem Y, Kokia E, Heymann AD, Porath A, et al. Persistence with statins and onset of rheumatoid arthritis: a population-based cohort study. *PLoS Med.* 2010; 7: e1000336.
- Chodick G, Weitzman D, Shalev V, Weil C, Amital H. Adherence to statins and the risk of psoriasis: a population-based cohort study. *British Journal of Dermatology.* 2015; 173: 480-487.
- Shovman O, Levy Y, Gilburd B, Shoenfeld Y. Anti-inflammatory and immunomodulatory properties of statins. *Immunol Res.* 2002; 25: 271-285.
- Gurevich VS, Shovman O, Slutzky L, Meroni PL, Shoenfeld Y. Statins and autoimmune diseases. *Autoimmun Rev.* 2005; 4: 123-129.
- May HT, Bair TL, Reiss-Brennan B, Knight S, Anderson JL, Horne BD, et al. The association of antidepressant and statin use with death and incident cardiovascular disease varies by depression severity. *Psychol Health Med.* 2017; 22: 919-931.
- Köhler-Forsberg O, Gasse C, Petersen L, Nierenberg AA, Mors O, Østergaard SD. Statin treatment and the risk of depression. *J Affect Disord.* 2019; 246: 706-715.
- Wood FA, Howard JP, Finegold JA, Nowbar AN, Thompson DM, Arnold AD, et al. N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Side Effects. *N Engl J Med.* 2020; 383: 2182-2184.
- Santos T, Baungratz MM, Haskel SP, de Lima DD, da Cruz JN, Magro DDD, et al. Behavioral interactions of simvastatin and fluoxetine in tests of anxiety and depression. *Neuropsychiatr Dis Treat.* 2012; 8: 413-422.
- Goodfellow NA, Almomani BA, Hawwa AF, McElroy JC. What the newspapers say about medication adherence: a content analysis. *BMC Public Health.* 2013; 13: 909.
- Mascitelli L, Pezzetta F, Goldstein MR. Detrimental effect of statin therapy in women with fibromyalgia. *Arch Intern Med.* 2008; 168: 1228-1229.
- Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J.* 2015; 36: 1012-1022.
- Mancini GBJ, Baker S, Bergeron J, Fitchett D, Fröhlich J, Genest J, et al. Diagnosis, Prevention, and Management of Statin Adverse Effects and Intolerance: Canadian Consensus Working Group Update (2016). *Can J Cardiol.* 2016; 32: S35-65.
- Thompson PD, Panza G, Zaleski A, Taylor B. Statin-Associated Side Effects. *J Am Coll Cardiol.* 2016; 67: 2395-2410.