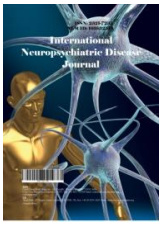

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The Relation of Vitamin D Blood Level with Statin-Associated Muscle Symptoms (SAMS)

Thouria Ijdayaat[1,2*], Khaled Eltoukhy[1,2], Maha Hazem[1,2] and Kefaya Elsyed[1,2]

[1]Department of Neurology, Mansoura University, Mansoura, Egypt.
[2]Department of Neurology, Mansoura New General Hospital, Mansoura, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. Author TI designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors KE and MH managed the analyses of the study. Author KE managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: This work evaluates the vitamin D status in patients with statins- associated muscle symptoms.
Study Design: A case control prospective study.
Place and Duration of Study: Neurology Department, Mansoura University, Mansoura, Egypt, between June 2020 and May 2021.
Methodology: Total of 85 participants included in this study, 60 participants of them have chronic Stroke and ischemic heart disease, treated by different kinds of statins and 25 participants were healthy controlled individuals. The 60 patients were 35 males (55%) and 25 females (45%), with age ranging from 40 to 70 years. The 60 participants were divided into two groups: The first group included (30 patients) treated with statins and they did not have Statin-Associated Muscle Symptoms (SAMS).The second group included (30 patients) also treated with Statin and they complained of SAMS. The third group is the control group, which contains the 25 participants who were healthy people. The control group included15 males (55%) and 10 females (45%) with age ranged from 35 to 65 years. Laboratory investigations were conducted on all participants in this study. The participants were subjected to total of 5 laboratory tests, which include: (1) Vitamin D

**Corresponding author: E-mail: thoraya.omer@su.edu.ly;*

(Enzyme immunoassay method), (2) Total CK (Enzymatic method), (3) Total Cholesterol and Triglycerides (Enzymatic method), (4)High density lipoproteins Cholesterol (Precipitation method), (4)Low density lipoproteins Cholesterol (Freid Wald equation), and (5) C – reactive protein (CRP: Latex Agglutination Method) was done beside elecetrophysiology study (Needle electromyography (NEMG) was include).

Results: Out of 60 patients the statistical readings of Vitamin D levels for the studied groups, demonstrating a significant statistical difference in Vitamin D levels between patients complaining of statin-associated muscle symptoms group (P≤0.001), and the other groups with lowest mean of (26.30 ±3.75), while patient without statin-associated muscle symptom group had the mean rating of (29.33 ±3.69), and the control group had the highest mean of (30.14 ±3.57).

Conclusion: There is a positive relationship between vitamin D deficiency and statin-associated muscle symptoms. Vitamin D status may play an important role in diagnosis and management of SAMS. Further studies are needed to evaluate the relationship between vitamin D and SAMS.

Keywords: The relation; vitamin D blood level; Statin-Associated Muscle Symptoms (SAMS).

ABBREVIATIONS

Here is the Definitions section. This is an optional section.

SAMS : Statin-Associated Muscle Symptoms;
HMGCoAR : Hydroxy-3-Methylglutaryl-Coenzyme A Reductases;
CPK : Creatine Phosphokinase;
CoQ10 : Coenzyme Q1O;
CRP : C-Reactive Protein;
CYP : Cytochrome P450;
CYP3A4 : Cytochrome P450 family 3 subfamily A member 4;
CYP2B6 : Cytochrome P450 family 2 subfamily B member 6;
CYP2C9 : Cytochrome P450 family 2 subfamily C member 9;
LDL : Low-Density Lipoprotein;
HDL : High-Density Lipoprotein;
NEMG : Needle Electromyography;
MUAPs : Motor Unit Action Potential;
SPSS : Statisticl Package for the Social Sciences;
SCIg : Subcutaneous Immunoglobulin;
25OH : 25Hydroxyvitamin D.

1. INTRODUCTION

Statins are the most commonly prescribed medication on the planet. Owing to recent decreases in the cardiovascular risk level, their use is expected to increase even further [1,2]. Statin myopathy, or statin-associated adverse muscle symptoms, is the most common side effect and the most common cause of therapy discontinuation [3].While statins are well tolerated, they can cause muscle weakness, muscle pain or aching (myalgia), stiffness, muscle tenderness, cramps, and arthralgia. Statin-Associated Muscle Symptoms (SAMS) are a group of symptoms that may occur with or without an increase in Creatine Kinase (CK) serum concentrations [4]. As well as more severe, potentially fatal outcomes (myositis and/or rhabdomyolysis) linked to elevated creatine kinase levels [5,6]. Vitamin D is a fat-soluble secosteroid that is absorbed and converted to Vitamin D3 in the skin when exposed to UV rays. The liver and kidneys then transform it to its active form [7]. The synthesis of Vitamin D begins with acetyl-CoA and proceeds through the cholesterol production process until 7-dehydrocholesterol is synthesized. Statins reduce cholesterol synthesis and 7-dehydrocholesterol and Vitamin D production by reversibly blocking the hydroxy-3-methylglutaryl-coenzyme A reductases (HMGCoAR), [8].

While Vitamin D levels in the blood influence muscle contractility, strength, and postural stability, the function of Vitamin D in SAMS is unknown. The main circulating metabolite of Vitamin D in the body, serum 25OH-Vitamin D, reflects Vitamin D inputs from cutaneous

synthesis and dietary intake. As a result, it is regarded as the gold standard clinical indicator of Vitamin D status [9]. Osteomalacia is a bone disorder that occurs when skeletal mineralization is compromised due to a lack of Vitamin D and/or the required substrate for hydroxyapatite formation (calcium and phosphate). Muscle weakness, pain, and hypotonia, particularly in children, are associated clinical features of this syndrome. Adults with serious, chronic Vitamin D deficiency (20 nmol/l) develop proximal myopathy, a waddling gait, and, in severe cases, the need for a wheelchair. Vitamin D deficiency causes muscle damage, which has been known for a long time [10].

Many statins patients experience muscle-related effects, preventing them from taking the prescribed doses. According to numerous studies [11], Muscle-related events were the most common explanation for statin therapy discontinuation. In clinical practice, statin therapy has been linked to muscle problems, especially myalgia and cramps, in about 10%–29% of patients [12]. Statin-related muscle adverse events include a wide variety of symptoms, from myalgias to uncommon life-threatening rhabdomyolysis. Creatine kinase (CK) elevation, usually 2 to 10 times the upper limit of the average, was seen in up to 5% of users [13]. Symptoms may appear at any time after beginning statin therapy, but they typically appear between 1 and 6 months [14]. Statins Myopathy is caused by a dosage , as well as high-intensity statin treatment are associated with an increased risk of muscle-related side effects, [15].

Statins work by inhibiting cholesterol synthesis. Statins can reduce vitamin D synthesis because endogenous vitamin D is derived from cholesterol. Furthermore, since atorvastatin (Lipitor), lovastatin (Altoprev and Mevacor), and simvastatin (FloLipidTM and Zocor) compete for the same metabolising enzyme, high vitamin D intake, particularly from supplements, can reduce the potency of these statins [16].

Low vitamin D levels have been linked to statin myopathy, as previously stated. Before resuming statin therapy, it is appropriate to determine vitamin D levels and, if possible, recommend substitution therapy. There is no conclusive proof that CoQ10 can help with the treatment or prevention of statin-related muscle side effects [17].

2. AIM OF THE STUDY

The aim of this study was to evaluate the Vitamin D status in 60 Egyptian patients and to determine if Vitamin D status can play any role in diagnosis and management of SAMS and see if there is any correlation between Vitamin D levels and SAMS.

3. METHODOLOGY

A case control prospective study was conducted on 85 participant 60 chronic patients of Stroke and ischemic heart disease, treated by different kinds of statins (rosuvastatin and atorvastatin 10-40mg) and 25 healthy controlled individuals. The study was carried out in Outpatient Clinics of Neurology & Cardiology with collaboration of laboratories of Clinical Pathology Department (Clinical Chemistry Unit), Neurology Department, Mansoura University, Mansoura, Egypt. The patients were 35 males (55%) and 25 females (45%), with age ranging from 40 to 70 years, in the period from June 2020 to May 2021. The study included three groups :The first group included (30 patients) treated with statins and they did not have Statin- associated Muscle Symptoms (SAMS).The second group included (30 patients) also treated with Statin and they complained of SAMS .The third group was the control group included 25 apparently healthy subjects: 15 males (55%) and 10 females (45%), their age ranged from 35 to 65years. They were age and sex matched and living in the same area and environment as patients.

These study groups were subjected to the following: full clinical and neurological assessment for all necessary details of both patients and control subjects. The inclusion criteria were as following: history of hypercholesterolemia, history of hypertension or cardiac diseases, history of cerebrovascular diseases, subjects treated with statin. The criteria of exclusion were as following: patients treated with Vitamin D, patients treated with corticosteroids, uncontrolled infectious disease, autoimmune disorders, diabetes mellitus, severe kidney dysfunction, hepatic disease history, malignancy, and therapy to replace hormones, hypo/hyperthyrodim, a history of alcohol abuse, patients in a vegetarian diet. Laboratory investigations: sampling collection, upon 12 hours of fasting conditions, five ml venous blood samples were obtained from peripheral vein by clean vein puncture under aseptic conditions using plastic disposable syringes onto plan tube:

(1) Vitamin D (Enzyme immunoassay method). (2) total CK (Enzymatic method).(3) total cholesterol and triglycerides (Enzymatic method). (4) high density lipoproteins Cholesterol (precipitation method).(4) low density lipoproteins Cholesterol (FreidWald equation). (5) C – reactive protein (CRP: Latex Agglutination Method).

Electrophysiology Study: needle electromyography (NEMG) with its major components: spontaneous activity, Motor Unit Analysis (MUAPs), recruitment, was done for the patient group in agreement with clinical findings & observe SAMS changes in the proximal muscles, which were: Shoulder Girdles (Bilateral Deltoid, Biceps Brachii &Triceps Muscles), limb girdles (Quadriceps, Bilateral Biceps Femoris). The healthy control group without any evident muscle symptoms and any history of muscle disease, they selected from (the blood bank donors.

4. RESULTS AND DISCUSSION

Our population is represented by total of 85 participant among of them 60 patients were on statin for several months. We conducted our study on cases from Outpatient Clinics of Mansoura University Hospitals. Our aim was to evaluate the Vitamin D status in 60 Egyptian patients. The study was done in one year duration. The patients were divided into two groups: group 1, which included 30 cases without statin-associated muscle symptoms and group 2, which included 30 cases with statin associated muscle symptoms. The two groups were then compared to 25 age and sex matched healthy controls group, as shown in Table 1. The results showed no statistical difference among age and gender between groups. The mean age in group 1 (patients on statin without SAMS) was 59.97 years with 50% males and the mean age in group 2 (patients with SAMS) was 55.73 years with 56% males. The mean age of the control group was 56.16 years with 60% males.

The statistical readings of Vitamin D levels for the studied groups, demonstrated a noticeable statistical difference in Vitamin D levels between group 2 and the other two groups. As can be seen from Table 1, group 2 had the lowest Vitamin D mean value of 26.30 ±3.75, while group 1 exhibited mean value of 29.33 ±3.69, and the control group had the highest mean of 30.14 ±3.57. This suggests that patients with SAMS will have lower Vitamin D level while those without SAMS will have higher level of Vitamin D. Moreover, the statistical readings of the lipid profile among the study groups indicate a major statistical difference in cholesterol levels between group 1 and the other two groups. Group 1 exhibited lower level of Cholesterol with median value of 69.5 while the Cholesterol level in group 2 and control group was much higher with median value of 101 each. An opposite trend can be noted between Vitamin D and Cholesterol level between the two groups. Patients with high level of Vitamin D exhibited lower level of Cholesterol and vis versa. In terms of Triglyceride levels, there were also important statistical differences among the groups studied. Group 2 exhibited the highest level of Triglyceride with a median value of 98.50 while group 1 and control group exhibited lower Triglyceride with median values of 67 and 68, respectively. This indicates that patients with lower level of Vitamin D had high levels of Cholesterol and Triglyceride levels.

Additionally, HDL level in group 1 was the lowest with a median value of 20.50, as compared to group 2 and control group, which exhibited higher HDL level with median values of 34.50 and 30, respectively. Similarly, LDL levels showed an increase in the control group and group 2 with median values of 58.8 and 32.4, respectively, while group 1 exhibited lower HDL level with median value of 25.3. Finally, statistical analyses of CPK & CRP levels in the study groups show also significant statistical difference between groups. For CPK, group 1 and group 2 exhibited higher levels of CPK with median values of 241 and 359.5, respectively while the control group showed the lowest level of CPK with median value of only 66.7.

The muscle symptoms and needle EMG results among group 2 are summarized in Table 2. The test results show that 8 patients who complained of Myopathy alone were the least among patients with statin-associated muscle symptoms, accounting for 26.7 %, while 11 patients who complained of both Myopathy and Myalgia or Myalgia alone were equal at 36.7%. Among the needle EMG of group 2, 20 patients had positive results of 66.7% and 10 patients had negative results of 33.35%.

The association between muscle symptoms, needle EMG results and serum Vitamin D in group 2 is shown in Table 3. As P-value indicates, there is no statistically significant difference between patients within this group.

Table 1. Demographic and laboratory data of the 2 patient groups and control group

Variable	*Group 1 (n=30)	*Group 2 (n=30)	Control group (n=25)
Age (years) Mean ± SD	59.97±8.39	55.73±8.39	56.16±6.49
Sex (%):			
Male (%)	50%	56.7%	60%
Female (%)	50%	43.3%	40%
Cholesterol(mg/dL) Median	69.50	101	101
Triglyceride(mg/dL) Median	68	98.50	67
HDL (mg/dL) Median	20.50	34.50	30
LDL (mg/dL) Median	25.3	32.4	58.8
CPK(IU/L) Median	241	359.5	66.7
CRP (mg/dL) Median	23	20	4
Vitamin D(nmol/L) Mean ± SD	29.33±3.69	26.30±3.75	30.14±3.57

**Group (1): Patient treated with Statins and they did not have Statin- Associated Muscle Symptoms*
**Group (2): Patient treated with Statins and they have Statin- Associated Muscle Symptoms*
** LDL: low-density lipoprotein; HDL: high-density lipoprotein; CPK: creatine phosphokinase; CRP: C-reactive protein*

Table 2. Muscle symptoms and needle EMG results among group (2)

	Group (2) (n=30)
Muscle symptoms	
Myopathy & Myalgia	11 (36.7%)
Myalgia	11 (36.7%)
Myopathy	8 (26.7%)
NEMG results	
Positive	20 (66.7%)
Negative	10 (33.3%)

Table 3. Association between muscle symptoms, needle EMG results and serum vitamin D

	Group (2)	
	Mean ± SD	**Test of significance (*P* value)**
Muscle symptoms:		
Myopathy & Myalgia	26.12±3.58	
Myalgia	26.54±3.67	$F = 0.035$
Myopathy	26.21±4.53	($P = .97$)
NEMG results:		
Positive	26.05±3.69	$t = 0.506$
Negative	26.80±4.02	($P = .62$)

**t: student t- test; *F: ANOVA test; *NEMG: Needle electromyography*

For muscle symptoms, the mean values were 26.12±3.58, 26.54±3.67, and 26.21±4.53 for Myopathy & Myalgia, Myalgia, and Myopathy, respectively. Similar observations for needle EMG results were noted between the positive and negative values of the mean.

Statins and CYP enzyme inhibitors have major drug–food interactions, suggesting a link between statin metabolism and the development of myopathy. Grapefruit juice stimulates CYP enzymes in the intestinal mucosa and liver, and statins combined with grapefruit juice have been linked to increased toxicity [18]. The inhibition of first-pass metabolism of lovastatin or simvastatin could result in 10–20-fold elevations (oral bioavailability increasing from 5% to 100%) in steady-state concentrations with a marked liability to drug toxicity. Other inhibitors of statin metabolism are cyclosporine, itraconazole, gemfibrozil, etc. The incidence of muscle disorder increases >10-fold when statins are given with these drugs [19]. Vitamin D activates CYP3A4, 1a, and 25-hydroxylase (OH) 2D3 is a CYP3A4 inducer in human hepatocytes, as researchers have previously discovered in intestinal cell lines. In primary human hepatocytes, the completely active

dihydroxylated metabolite of vitamin D3 induces the expression of not only CYP3A4 but also CYP2B6 and CYP2C9. 3-hydroxy-3-methylglutaryl-Coenzme A (HMG-CoA) reductase activity is also present in hydroxylated vitamin D derivatives [20].

The CYP enzyme inhibitors increase the toxicity of CYP metabolised statins, while CYP enzyme inducers improve metabolism and produce fewer toxic metabolites [18]. Since vitamin D is a CYP3A4 and CYP2C9 inducers, it is likely that it will aid in the metabolism of some statins, lowering their toxic side effects. This is exactly what the previously reported papers and studies have found [21]. Since CYP3A4 and CYP2C9 are both involved in the oxidative metabolism of statins, the chemical nature and pharmacological activity of the metabolites vary widely. Every statin drug's metabolic rate, as well as the effect of that metabolism on potency and period of action, must be assessed separately. The increased enzyme activity and decreased toxicity of atorvastatin after vitamin D supplementation was explained by the fact that vitamin D is a recognised inducer of CYP3A4 and the metabolites are responsible for pharmacological activity. Lovastatin and simvastatin have inactive CYP3A4 metabolites. Since CYP3A4 metabolism inhibition causes increased toxicity [22].

In this study and as can be seen in Table 4, group 2 showed deficiency in Vitamin D levels among the patients with SAMS compared to that in group 1 for patients without SAMS. The significant difference between the two groups was (P = 0.003), another significant difference was observed between group 2 and control group with ($P \leq 0.001$). These results are in line with the finding of other study performed in 2019 by Pennisi, et al., where they reported a significant association between Vitamin D deficiency and the muscular symptoms due to statin therapy, where value of ($P < .0001$) was reported [9].

Some studies have showed that, Vitamin D deficiency can lead to an increased susceptibility to the development of SAMS; and recorded that a 1.22-fold increase in the risk of SAMS occurred every 1 ng/mL decrease in Vitamin D levels and indicated that the Vitamin D deficiency impairs the lipid reactance of statins and increases the risk of myopathy in statin users [23,24]. On other hand, further studies have indicated that statins increased serum 25-OH D levels, while others reported that statins have no effects on levels of Vitamin D [25,26].

Moreover, no correlation was found with Vitamin D serum levels in both patients' groups. This comes in agreement with the findings of other study, which identified no impact of statin was found on 25-OH D level, at any dose, of more than one year duration. Similar negative results were obtained from 63 dyslipidemic patients received statin for 12 weeks [27,28].

In addition, we did not detect any significant difference among the duration of statin use. The mean duration was 9.5 (1-30 months) in group 1 and 12 (1-60 months) in group 2, with no significance difference observed (P = .42). The same found for the dose of statin, the mean value was 23.00 for patients without SAMS & 20.67 for patients with SAMS, (P = .24). The statin dose used ranged from 10mg to 40mg for the two patient groups. In contrast, some research demonstrated, in cell culture experiments, that inhibition of osteoclastic activity was inversely correlated with the magnitude of HMG-CoA reductase activity of statins, thus suggesting that higher-intensity statins could be more effective in modifying Vitamin D levels [29].

Table 4. Test of significance for demographic and laboratory data of patient groups

variable	P1	P2	P3
Age (years) Mean ± SD	(P = 0.081)	(P = 0.084)	(P = 0.06)
Sex (%)	(P = .46)	(P = .81)	(P = .61)
Cholesterol(mg/dL)	(P = .03)	(P = .76)	(P = .019)
Triglyceride(mg/dL)	(P = .63)	(P = .001)	(P = .008)
HDL (mg/dL)	(P = .006)	(P = .25)	($P \leq$ .001)
LDL (mg/dL)	(P = .005)	(P = .023)	(P = .56)
CPK(IU/L)	(P = .001)	(P = .001)	(P = .01)
CRP (%)	(P = .16)	(P = .26)	(P = .86)
Vitamin D(nmol/L) Mean ± SD	(P = .42)	($P \leq$ .001)	(P = .003)

**P1: Comparison between Group (1) and control; *p2: Comparison between Group (2) and control; *p3: Comparison between Group (1) and Group (2); * LDL: low-density lipoprotein; HDL: high-density lipoprotein; CPK: creatine phosphokinase; CRP: C-reactive protein*

Furthermore, as indicated in Table 4, Vitamin D status may affect lipid changes during statin therapy. In the comparison between SAMS patients and patients without SAMS (i.e., P3), we observed a significant difference in Cholesterol (P = .019), Triglyceride (P = .008), and HDL (P < .001). However, LDL did not show any significant correlation with Vitamin D deficiency (P = .56). This contrasts with some studies who have reported different results for LDL and suggested that a significant correlation between the lipid-lowering effectiveness of statins and Vitamin D levels has been detected [19]. Additionally, we observed a statistically significant difference in CPK levels between the two patient groups studied (P = .01). However, CRP result did not show any statistically significant correlation with Vitamin D deficiency (P =.86). This agrees with the findings reported in a previous published study [30].

Table 5 shows a statistical analysis of the duration of Statin use in months by two patient groups. The data indicating that there was no statistically significant difference in the duration of the two groups (P = .42), with the median duration being 9.5 in the group (1) compared to 12 in the group (2). Furthermore, Table 5 shows statistical details about the Statin doses used by the two patient groups, demonstrating that there was no statistically significant difference in the doses used by the two groups of patients, (P = .24). Group (1) had a mean of 23.00 ±9.15, while group (2) had a mean of 20.67 ±5.83. This in agreement with [30], which identified no impact of statin at any dose, for duration of more than one year on 25-OH D level. Moreover, similar negative results were reported by [31], who conducted 63 dyslipidemic patients, receiving statin for 12 weeks. In contrast other studies [29] research demonstrated in cell culture experiments, reported that a higher-intensity statins could be more effective in modifying vitamin D levels.

The clinician used an electrophysiological study to perform a noninvasive screening for a possible drug-induced myopathy at the time of onset as well as during follow-up visits (test for reversibility) [32]. Both SAMS patient groups had subacute and persistent proximal weakness affecting the shoulder and lower limbs, as well as difficulty combing hair, climbing stairs, and standing from a squatting position, as well as diffuse myalgia and muscle cramps, with 36.7% having both myopathy and myalgia.

In this study, we have reported 36.7% of patients had myalgia, and 26.7% had only myopathy. Needle EMG performed on the deltoid, biceps, triceps, quadriceps, and biceps femoris showed irregular spontaneous activity, such as fibrillation potentials and positive sharp waves with short, weak, and polyphasic motor unit action potentials (MUAP), indicative of muscle dysfunction, in 66.7%, while 33.3% showed no changes. The majority of the motor unit action potentials (MUAPs) were short in length and amplitude, suggesting a myogenic origin. The majority of MUPs had a low amplitude. The number of recruits has decreased slightly.

In consistent to other study retrospectively analyzed clinical records of patients with immune-mediated necrotizing anti-HMGCR myopathies treated with SCIg from 2018 to 2020 and found the same finding according to Needle EMG performed on the deltoid, biceps, and quadriceps [33].

Finally, according to SAMS patient group we studied the relation of Vitamin D level among each muscle symptom, we observed non-significant differences between every muscle symptom and Vitamin D level (P = .96). Moreover, we studied the relation between Vitamin D level and needle EMG results, also we found no significant correlation (P = .61). See Table 2.

Table 5. Dose of statin by mg and duration in months of statin use among studied groups

Durations and doses of Statin use	Group (1) (n=30)	Group (2) (n=30)	Test of significance (p value)
Duration of Statin use (by months)			
Median (Min-Max)	9.5 (1-30)	12 (1-60)	Z=0.801 (P=.42)
Dose of statin(mg)			
Mean ± SD	23.00±9.15	20.67±5.83	t=1.18 (P=.24)

Z: Mann Whitney test; t: student t- test

Group (1): Patient treated with Statins and they did not have Statin- Associated Muscle Symptoms

Group (2): Patient treated with Statins and they have Statin- Associated Muscle Symptoms

5. CONCLUSION

Our study findings support earlier suggestions of a positive relationship between Vitamin D deficiency and statin-associated muscle symptoms. Vitamin D status may play an important role in diagnosis and management of SAMS. Further studies are needed to evaluate the relationship between Vitamin D and SAMS.

6. LIMITATIONS

Because our study a case control prospective, conclusions regarding definitive linkage and causality cannot be drawn. Patients were not on a standardized statin regimen; therefore, it may be that a certain statin did not interact with Vitamin D pathways resulting in the absence of SAMS. Furthermore, due to the small sample size, individual statins could not be assessed against Vitamin D to identify independent associations; however, even with the small sample size, a statistically significant relationship was observed between the two groups. Moreover, the collection of samples done during the pandemic period of corona virus, which limited our work regarding NEMG for all patient groups. Finally, we did not collect data at follow-up, therefore, we did not evaluate whether Vitamin D supplementation could improve the SAMS.

CONSENT

Written informed consent was obtained from all individual participants included in the study.

ETHICAL APPROVAL

The Institutional Revision Board (IRB) of Mansoura University approved the study protocol on 3.06.2020, Code Number: MS.20.05.1118. For human research to determine the possibility of Vitamin D levels may be useful for the diagnosis and management of SAMS.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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