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## ASSOCIATION OF VITAMIN D WITH STATIN INDUCED MYALGIA

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## ABSTRACT

**Objective:** To determine the association of serum 25-hydroxy vitamin D (25(OH) Vitamin D) deficiency with the occurrence of myalgia in patients on statin therapy. **Methods:** The pathology laboratory database was reviewed to identify patients tested for serum 25(OH) Vitamin D and creatine kinase. A retrospective chart review was then conducted to ascertain statin use and reporting of myalgia for patients tested concurrently for serum 25(OH) vitamin D and creatine kinase levels between January 1, 2013 and December 31, 2013. **Results:** Of the 825 patients tested for creatine kinase and 25 (OH) Vitamin D in 2013, 49 met the study criteria. The mean serum 25 (OH) Vitamin D level in the 24 statin induced myalgia patients was  $17.93 \pm 12.07$  compared to  $18.99 \pm 15.2$  in the 25 no SIM group ( $p = 0.81$ ). **Conclusion:** Our study reports no association between statin induced myalgia and low 25 (OH) vitamin D levels.

**Key words:** Statin, Myalgia, Vitamin D deficiency

## INTRODUCTION

Statins are considered safe and effective drugs that are prescribed frequently for their lipid lowering capabilities to prevent atherosclerosis and coronary vascular disease<sup>(1)</sup>. The most common complaint associated with statin use and their discontinuation is muscle pain, which ranges in severity from myalgia to rhabdomyolysis<sup>(2,3,4)</sup>. Presently there is no known treatment that can conclusively achieve resolution of statin induced myalgia (SIM) and allow continuation of the lipid lowering therapy. A few recent studies have indicated a possible potentiating effect of vitamin D deficiency on the development of SIM<sup>(5,6)</sup> and improvement in statin tolerance following supplementation and normalization of serum vitamin D levels in most deficient patients<sup>(7,8)</sup>. The purpose of this study is to identify patients with SIM and evaluate their 25 (OH) vitamin D levels with the aim of determining the presence or absence of an association between the two.

## MATERIALS AND METHODS

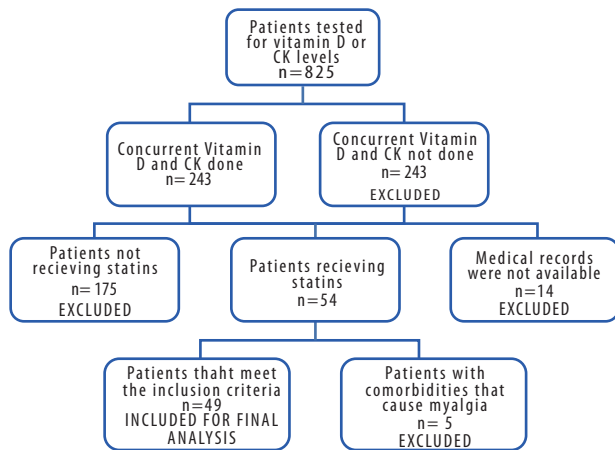
This study was approved by the Shifa International Hospital Institutional Review Board and Ethics Committee. This retrospective review of the pathology laboratory data-

base was conducted from January 1, 2013 to December 31, 2013 in order to identify patients tested for serum 25-hydroxyvitamin D (25(OH) Vitamin D) and concurrent Creatin Kinase (CK) levels. This was followed by a chart review of the patients to confirm statin use and reporting of myalgia at the time of ordering of these laboratory investigations. The 25(OH) Vitamin D levels are determined at our laboratory by Chemiluminescent-microparticle immunoassay (CIMA) using the ARCHITECT System by Abbott laboratory. The normal values of 9.5 up to 55.5ng/ml are used based on a study conducted according to the Clinical Laboratory and Standards Institute, Protocol C28-A3(9). CK levels were determined using ARCHITECT c SYSTEMs and the AEROSSET System by spectrophotometry. A normal range of 30-200U/L for males and 29-168U/L for females is used<sup>(10)</sup>. All patients receiving statin therapy who had their 25(OH) vitamin D and CK levels checked were included in the study. Patients with diagnosed malignancy, chronic liver disease, rheumatoid arthritis and sarcoidosis were excluded from this study. Statistical analysis was performed using IBM SPSS Statistics Data Editor, v21. Categorical variables were assessed using the Chi squared test. Association of 25(OH) Vitamin D with SIM was calculated using logistic regression with adjustment for age and CK

levels. For all statistical tests a p-Value of <0.05 was considered significant.

## RESULTS

Between January 1, 2013 and December 31, 2013 a total of 825 patients (Figure 1) were tested for 25(OH) Vitamin D and CK at the SIH pathology laboratory. 243 of these patients were tested concurrently. We identified 54 of these 243 patients to have received Statin therapy, 175 did not and the medical records of 14 were not available for review. Overall 54 patients met the study criteria while 5 patients were excluded due to their co-morbidities (3 with Rheumatoid Arthritis, 1 with Non-Hodgkin's Lymphoma and 1 with Chronic Hepatitis B). 49 patients were included for final analysis.



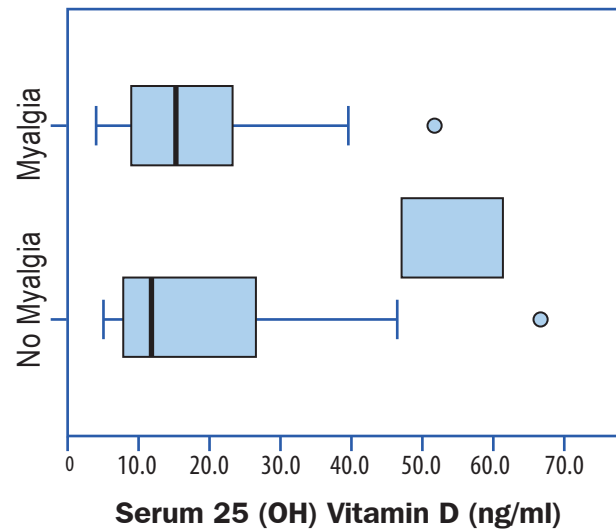
**Figure 1.** Flow Chart of Patient Selection

The 49 patients receiving statins were divided into two groups based on presence or absence of myalgia. Differences between the two study groups were minimal except for age, with the mean  $\pm$  standard deviation (SD), in the SIM and no SIM group of  $58.38 \pm 10.12$  and  $67.08 \pm 10.04$  ( $p = 0.01$ ), respectively (Table 1). Analysis of the serum 25(OH) Vitamin D also revealed little difference between the two groups. The mean serum 25(OH) Vitamin D level in the 24 SIM patients was  $17.93 \pm 12.07$  compared to  $18.99 \pm 15.2$  in the 25 no SIM group ( $p = 0.81$ ). Evaluation of the prescribed statin, the dose and patient comorbidities also failed to show significance.

## DISCUSSION

Statin associated muscle adverse reports range from 1% to 5% in controlled clinical trials to 11% to 29% in observational cohorts<sup>(11)</sup>. This discrepancy between numerous studies may be due to lack of standard

definitions that can identify statin induced muscle problems, making it difficult to assess the true percentage of these adverse effects<sup>(11, 12)</sup>. Our study however, showed a higher percentage (49%) of myalgia because we only assessed patients that were tested for CK instead of a random population of statin users. Considerable debate exists regarding the factors influencing occurrence of SIM, indicating a multifactorial etiology<sup>(13)</sup>. To that effect we took into account patient's age, gender, CK, specific statin used, dosage and co-morbidities along with the 25(OH) Vitamin D levels. Although our analysis shows a significant difference in patient age between the SIM and no SIM group ( $58.38 \pm 10.12$  and  $67.08 \pm 10.04$  ( $p = 0.01$ )), the mean age was higher in group with no myalgia, which is contrary to the effects of advancing age on the development of myalgia<sup>(14)</sup>.



The remaining variables showed no significant difference between the two study groups. Similar to the concern regarding factors affecting SIM, there is also substantial variation in the range of 25(OH) Vitamin D levels that are considered normal. While our laboratory reports a normal range of 9.5-55.5 ng/ml, the Mayo Medical Laboratories adopts <10ng/ml (severe deficiency), 10-24ng/ml (mild – moderate deficiency), 25-80ng/ml (optimal) and >80ng/ml (possible toxicity)<sup>(15)</sup>. Several studies have defined vitamin D deficiency as circulating levels of less than 80nmol (32ng/ml)<sup>(16)</sup>. We report 21(87.5%) patients with low 25(OH) vitamin D (<32ng/ml) in the SIM group and 21(84%) in the no SIM group with an overall 42(85.71%) patients ascertained to be vitamin D deficient. Of these patients 6(25%) and 9(36%) have severe 25(OH) vitamin deficiency (<9.5ng/ml) in the SIM and no SIM group, respectively. The current report revealed that the SIM group did not have a significantly lower vitamin D level

(Figure 2). Logistic regression of myalgia and vitamin D, taking age and CK as covariates, showed no association between vitamin D levels and occurrence of SIM.

	SIM	No SIM	p-Value
n (%) or mean ± SD	24 (49)	25 (51)	-/-
Gender	12 (50)	14 (56)	0.67*
Male	12 (50)	11 (44)	
Female			
Age	58.38 ± 10.12	67.08 ± 10.04	0.01*
Diabetes Mellitus	16 (66.7)	15 (60)	0.63*
Hypertension	17 (70.8)	17 (68)	0.83*
Coronary Artery Disease	9 (37.5)	10 (40)	0.86*
25 (OH) Vitamin D	17.93 ± 12.07	18.99 ± 15.2	0.81*
CK	201.17 ± 425.45	106.2 ± 62.12	0.63*
Atorvastatin	8 (33.3)	11(44)	0.44*
5mg	0 (0)	0 (0)	-/-
10mg	6 (75)	7 (63.64)	0.81*
20mg	2 (25)	4(36.36)	0.41*
Rosuvastatin	16 (66.7)	11(44)	0.11*
5mg	6 (37.5)	3 (27.27)	0.24*
10mg	6(37.5)	7 (63.64)	0.81*
20mg	4 (25)	1 (9.09)	0.14*
Simvastatin	0 (0)	3 (12)	0.08*
5mg	0 (0)	0 (0)	-/-
10mg	0 (0)	2 (66.67)	0.16*
20mg	0 (0)	1 (33.33)	0.32*

**Figure 2.** Comparison of Myalgia and 25(OH) Vitamin D

These findings are consistent with several previously reported analyses<sup>(17-20)</sup>. A literature review<sup>(3)</sup> also found no definitive evidence that vitamin D deficiency contributes to statin myalgia. In contrast, numerous studies show potential reversibility<sup>(8,21)</sup> or resolution of myalgia symptoms in statin treated patients after vitamin D supplementation to levels within normal range<sup>(7,8,22)</sup>. Shantha et al. concluded that low vitamin D level (<15 ng/ml) at statin initiation are associated with and have a high predictive accuracy for SIM although randomized controlled trials are required to validate these results. This disparity in analyses may be

due to small sample size, lack of randomization, absence of a validated scale to identify SIM, genetic variation, regional differences or a multitude of other factors that influence SIM. Further evaluation of this perplexing interaction between vitamin D and SIM is required to reach a definitive conclusion.

## CONCLUSION

The limitations of our study were a small sample size comprising a majority of patients with low vitamin D (<32ng/ml). We found no association between low 25(OH) vitamin D levels and statin induced myalgia. There is need for a randomized double blind placebo controlled trial to obtain conclusive evidence regarding the influence, if any, of vitamin D on this statin induced myalgia.

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**Author's contribution:**

**Dr. Arsalan Ahmed:** Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review

**Dr. Imran N Ahmed:** Data collection, data analysis, manuscript writing, manuscript review

**Dr. Ayla K Zubair:** Data collection, data analysis manuscript review