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A Comparative Study Of Serum Creatine Kinase Of Patients On Statins Before And After Supplementation Of Vitamin D3 Orally In A Tertiary Care Hospital.

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ABSTRACT

Raised cholesterol increases the risks of heart disease and stroke. Globally, a third of ischaemic heart disease is attributable to high cholesterol. Overall, raised cholesterol is estimated to cause 2.6 million deaths and 29.7 million disability adjusted life years (DALYS). Raised total cholesterol is a major cause of disease burden in both the developed and developing world as a risk factor for ischemic heart disease and stroke. A 10% reduction in serum cholesterol in men aged 40 has been reported to result in a 50% reduction in heart disease within 5 years. The prevalence of elevated total cholesterol was 29% for the South East Asian Region. Statins inhibit cholesterol synthesis via blockade of the enzyme 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase. Consequently, the inability of the liver to make its own cholesterol results in the upregulation of LDL receptor expression, which lowers plasma LDL cholesterol levels. Statins can lower LDL-C close to 50 %, and can also cause HDL-C elevations of around 5–10 % and triglyceride reductions of 15–30 %. Statins can cause creatine phosphokinase (CPK) levels to be mildly elevated; CPK is a muscle enzyme that can be measured in the bloodstream. Muscle pain, mild inflammation, and possible weakness are seen. The clinical spectrum of statin induced myopathy includes myalgia, myositis, rhabdomyolysis, and an asymptomatic increase in the concentration of creatine kinase. vitamin D deficiency may decrease nuclear vitamin D receptor linked gene transcription and subsequent synthesis of proteins required for repair of the T-tubular system and prevention of subsarcolemmal rupture. Other possibilities are that statins most commonly associated with myalgia (atorvastatin) are metabolized by CYP3A4, which displays 25-hydroxylase activity in vitro. Vitamin D deficiency may lead to 'preferential shunting' of CYP3A4 for hydroxylation of vitamin D, reducing availability of CYP3A4 for statin metabolism, leading to statin-induced toxicity. Statin intolerance because of myalgia, myositis, myopathy, or myonecrosis in vitamin D deficient patients can, in most cases (88%-95%), be safely resolved by vitamin D supplementation (50,000-100,000 units/week).

Keywords: Statin, CPK, Myopathy, Vitamin D Deficiency.

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INTRODUCTION

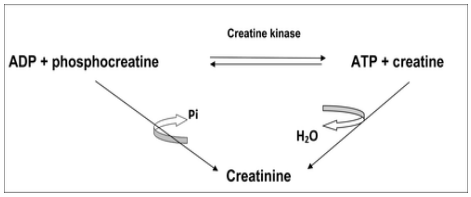
Ischemic heart disease (IHD) is a leading cause of death worldwide. It is also referred as coronary artery disease (CAD) and atherosclerotic cardiovascular disease (ACD), it manifests clinically as myocardial infarction and ischemic cardiomyopathy. Ischaemic Heart Disease affects around 126 million individuals (1,655 per 100,000), which is approximately 1.72% of the world's population. Nine million deaths were caused by IHD globally. Men are more commonly affected than women, and incidence typically starts in the fourth decade and increases with age. The global prevalence of IHD is rising. We estimated that the current prevalence rate of 1,655 per 100,000 population is expected to exceed 1,845 by the year 2030. Coronary heart disease prevalence rates in India have been estimated over the past several decades and have ranged from 1.6% to 7.4% in rural population and from 1% to 13.2% in urban population [1]. One of the important risk factors for ischaemic heart disease is dyslipidaemia.

Raised cholesterol increases the risk of heart disease. Globally, a third of ischaemic heart disease is attributable to high cholesterol. It is a major cause of disease burden in both developed and developing countries. A 10% reduction in serum cholesterol in men aged 40 has been reported to result in a 50% reduction in heart disease within 5 years [2]. Statins are the mainstay of treatment of dyslipidaemia.

Statins inhibit cholesterol synthesis by competitively inhibiting the enzyme 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA reductase) [2]. This results in inability of the liver to make its own cholesterol that leads to an increase the number of low-density lipoprotein receptor expressions (upregulation). Thus. reduction in the plasma LDL levels achieved. Statins are the powerful drugs that lower LDL-C by close to 20- 50 % and can also cause elevations of plasma HDL-C levels of around 5–10 %. Statins also produce a moderate reduction in triglyceride levels (15–30 %.).

Statins can also cause creatine phosphokinase (CPK) levels to be mildly elevated; CPK levels can be measured in the bloodstream. Muscle pain, mild inflammation, and possible weakness are seen with the use of statins. The clinical spectrum of statin-induced myopathy is classified as myalgia, myositis, rhabdomyolysis, and an asymptomatic increase in the levels of plasma creatine phosphokinase.

Creatine phosphokinase (CPK), also known by the name creatine kinase (CK), is the enzyme that catalyses the reaction of creatine and adenosine triphosphate (ATP) to phosphocreatine and adenosine diphosphate (ADP). The phosphocreatine created from this reaction is used to supply tissues and cells that require substantial amounts of ATP, like the brain, skeletal muscles, and the heart [3].



Levels of CPK can rise after a skeletal muscle injury or strenuous exercise. and is considered the best marker for the detection and monitoring of skeletal muscle diseases [4]. The creatine kinase levels can also go up after drinking too much alcohol or from taking certain medications. Among statins Atorvastatin is the preferred drug.

There is a strong correlation between the low serum Vitamin D levels and higher incidence and longer duration of muscle aches and pains (diagnosed as fibromyalgia) on patients treated with statins were reported by Erkal et al [5].

Vitamin D binds to a cytoplasmic vitamin D receptor and translocate to the nucleus. There it increases the specific mRNA synthesis which regulates protein synthesis. Vitamin D deficiency may lead to a reduction in this receptor linked gene transcription. This may lead to a decrease in the synthesis of proteins that are required for the T-tubular system repair and prevention of subsarcolemmal rupture.

Other possibilities are that statins particularly atorvastatin most associated with myalgia are metabolized by CYP3A4. Deficiency of Vitamin D may lead to preferential shunting of the enzyme CYP3A4

for Vitamin D hydroxylation. It results in a reduction of CYP3A4 for the metabolism of statins which leads to statin-induced toxicity [6].

Several studies supported that functional responses in skeletal muscle were influenced by mechanisms that could be affected by biological effects of an active form of vitamin D and also its ability to bind with the membrane and nuclear vitamin D receptors (VDRs) [7]. There is a significant association between serum levels of 25(OH) vitamin D and muscle fatigue biomarkers in which serum 25(OH)Vitamin D levels correlated positively with serum calcium level and negatively with CPK and VAS score respectively [8].

Many Interventional studies have shown that supplementation with vitamin D 50,000 IU/week, may have protective effects against myalgia in statin treated patients [9].

Our specific aims were to determine whether there is a decrease in serum Creatine Kinase levels in patients taking statins associated with myalgia and vitamin D supplementation could reverse myalgia while continuing statins.

Aim And Objectives

Aim

The purpose of the study was to estimate the serum creatine kinase levels in patients taking statins associated with myalgia before and after supplementation of vitamin D3 orally.

Secondary Objective

To study the correlation between vitamin D supplementation and serum creatine kinase level

MATERIALS AND METHODS

Sample size: census sampling during the period of study.

Study design: Cross-sectional study.

Study Place: Cardiology OPD, Tirunelveli medical college and hospital.

Study population: Patients on statins associated with myalgia with elevated serum creatine kinase attending the Cardiology OPD during the period of study.

Study period: July 2020 to June 2021.

Study duration: 1 year.

Inclusion Criteria

- Age between 20 -60 of both sexes
- Patients on Tab. Atorvastatin 10-80mg daily of less than 2 years duration
- Patient associated with myalgia (Myalgia can be defined as new or increased muscle pain, cramps, or aching, not associated with exercise; Symptoms persisted for at least 2 weeks) [10].

Exclusion criteria

- Pregnancy and lactating mothers.
- Paediatric patients aged below 18.
- Abnormal hepatic and renal parameters.
- Post CABG patients.
- Poor glycaemic control and immuno-compromised patients
- Hypothyroid patients
- Patients on steroids

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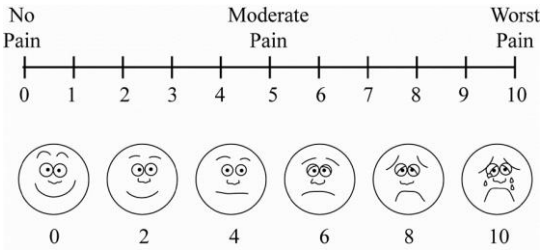
Ethical Approval

Institutional Ethical Committee (IEC) clearance was obtained prior to study commencement. The patients who were attending cardiology OPD were recruited for this study. All the subjects were clearly explained about the study in their language. Written and Informed consent was obtained from those who were willing to participate in this study.

Methodology

Patients attending the cardiology outpatient department with treatment on statins for less than 2 years were evaluated. Patients associated with myalgia using a Visual Analogue Score of 6 and above were selected for the study. Information on demographic characteristics (which include age, occupation, economic status), Family history, Personal history and medical history with comorbidities were collected using questionnaires and face-to-face interviews. Relevant clinical examinations were done. Vitals were recorded including pulse rate and blood pressure. Complete blood count, blood sugar, lipid profile and serum creatine kinase estimation were done for all the patients. These participants were supplemented orally with Tab. Vitamin D3 50000IU/ fortnightly for 12 weeks along with the statins. Patients were reviewed after 4, 8, 12 weeks of follow up on the 24th week. Patients were recorded blood pressure; pulse rate and myalgia were assessed by visual analogue score on each review. Patients' compliance with vitamin D3 were noted. Serum creatine kinase levels were estimated on enrolment, after 12 weeks and 24 weeks. Patients were allowed to take other medicines for associated conditions like diabetes mellitus, hypertension.



Materials

- Weighing Scale: Krups, made in India.
- Mercury Sphygmomanometer: Diamond, made in India.

Measurement of weight

Using a portable Krups body weighing scale, the Participant's weight was measured in kilograms after being adjusted to zero level. The participants were advised to be in light clothing and remove all belongings.

Measurement of Blood Pressure

The Participants were quietly seated for 5 minutes' period and BP was measured on both the arms using a standard mercury sphygmomanometer (Diamond, made in India) at heart level using appropriate cuff size. BP readings were recorded after the mercury column was adjusted to the Zero position.

Estimation of Serum Creatine kinase

Method: Oliver method, Erba Assay.

Principle

The rate of absorbance change at 340 nm is directly proportional to creatine kinase activity.

$$\text{Creatine phosphate} + \text{ADP} \xrightarrow{\text{CK}} \text{Creatine} + \text{ATP}$$

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Reference Values

At 37^0 C (U/L)

- Males: 46-171 U/L
- Females: 24-145 U/L

RESULTS

The study was conducted on 30 participants who were taking tab. Atorvastatin 10 to 80 mg for less than 2 years duration and estimation of serum creatine kinase levels before and after supplementation of vitamin D3.

Statistical Analysis

- The data was analysed using SPSS (Statistical Package for Social Science) version 21.0 (IBM-SPSS Science Inc. Chicago, IL)
- Continuous variables were compared using a paired sample t-test.
- Pearson correlation tests were used for correlation.
- Significance was defined by P values less than 0.05 using a two-tailed test.

Age Distribution Of The Study Participants

Table 1

Age Distribution in years	No. of participants	Percentage
< 40	5	16.7
41 - 50	5	16.7
51 - 60	20	66.7
Total	30	100.0

Table 1 shows the data of the age distribution of the study participants. The minimum age was 34 and the maximum age participated was 60 with a mean of 51.53±7.94 years

	Minimum	Maximum	Mean	Std. Deviation
AGE IN YEARS	34.00	60.00	51.53	7.94

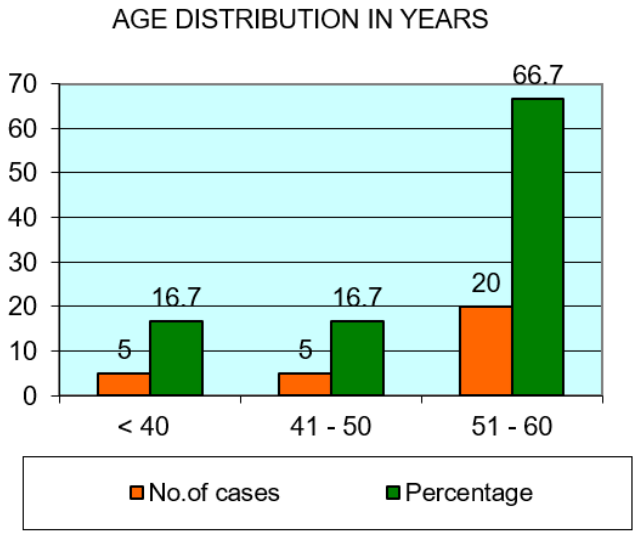

Figure 1: Age Distribution Of The Study Population In Years

In my study population majority of the patients are in the age group of 41-50 years and 51-60 years of 16.7% and 66.7% respectively.

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Sex Distribution Of The Study Participants

Table 2

SEX	No. of participants	Percentage
Female	6	20.0
Male	24	80.0
Total	30	100.0

Table 2 shows the data of sex distribution of the study participants in my study majority of the participants are male with 80% and female of 20%.

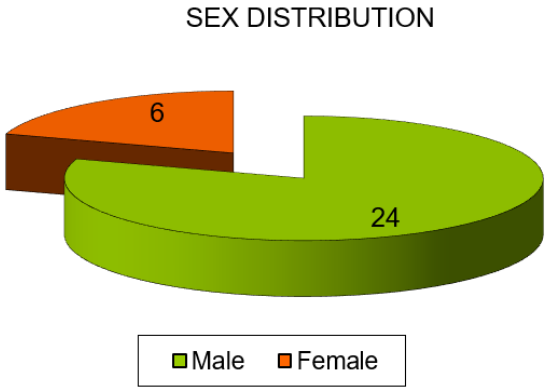

Figure 2: Sex Distribution Of The Study Population

Locality Distribution Of The Study Participants

Table 3

LOCALITY	No. of participants	Percentage
Urban	10	33.3
Rural	20	66.7
Total	30	100.0

Table 3 shows the data of the locality distribution of the study participants. In my study, the majority of the patients are from a rural area with 67%, while the urban population was 33%.

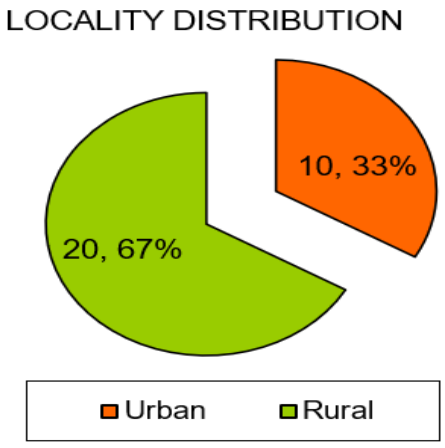

Figure 3: Locality Distribution Of The Study Population

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EDUCATION STATUS OF THE STUDY PARTICIPANTS

Table 4

EDUCATION	No. of participants	Percentage
Primary	3	10.0
High school & higher secondary school	24	80.0
Diploma & degree	3	10.0
Total	30	100.0

Table 4 shows the data of education status of the study participants.

In my study participants, the majority of them (80%) were completed high school and higher secondary school education

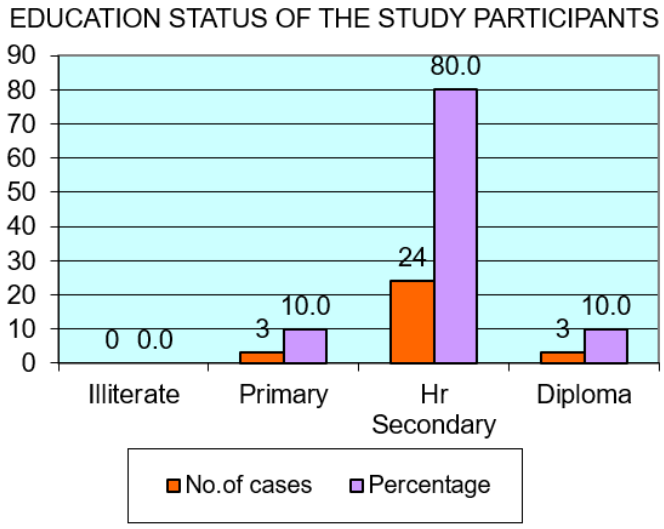

Figure 4: Education Status Of The Study Population

Occupation Distribution

Table 5

OCCUPATION	No. of participants	Percentage
UNEMPLOYED	5	16.7
UNSKILLED	7	23.3
SEMISKILLED	17	56.7
SKILLED	1	3.3
Total	30	100.0

Table 5 shows the data of occupation of the study participants.

In my study participants, the majority were semiskilled and unskilled around 56.7% and 23.3% respectively.

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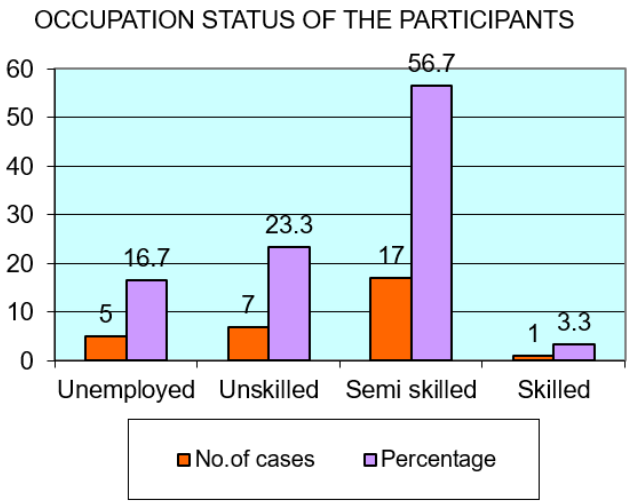

Figure 5: Occupation Status Of The Study Population

SOCIO ECONOMIC STATUS

Table 6

SOCIO-ECONOMIC STATUS	No. of Participants	Percentage
Lower	11	36.7
Middle	19	63.3
Total	30	100.0

Table 6 shows the data of the socio-economic status of the study participants. The majority of them (63.3%) were middle belongs to the middle socioeconomic status group.

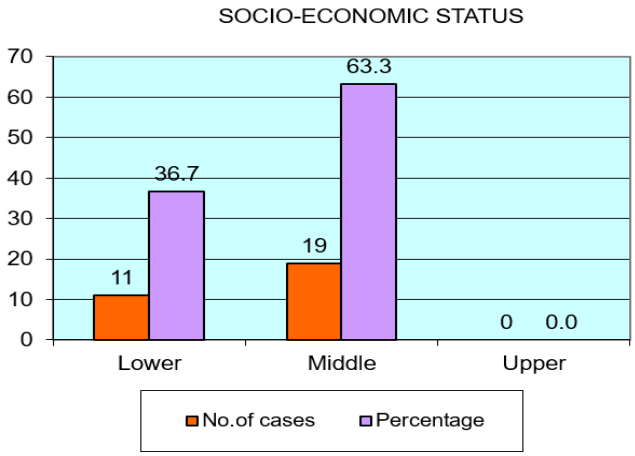

Figure 6: Socioeconomic Status Of The Study Population

Substance abuse in the past year

Table 7

SUBSTANCE ABUSE IN PAST ONE YEAR	Frequency	Percentage
Smoker	3	10.0
Alcoholic	3	10.0
Smoker and Alcoholic	3	10.0
None	21	70.0
Total	30	100.0

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Table 7 shows the data of substance abuse of the study participants in the past year. About 10% of them were smokers, 10% of them were alcoholics and another 10% were both smokers and alcoholics.

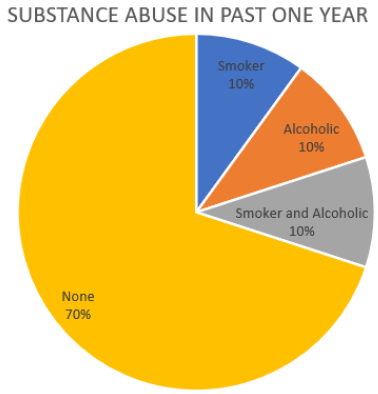

Figure 7: Substance Abuse In The Past Year Of The Study Population

Comorbidities Of The Study Population

Table 8

DIAGNOSIS	Frequency	Percentage
CAD	12	40.0
CAD/ACS	1	3.3
CAD/ACS/T2DM	1	3.3
CAD/DM	8	26.7
CAD/DM/HT	5	16.7
CAD/HT	3	10.0
Total	30	100.0

Table 9 shows the data of comorbidities of the study participants.

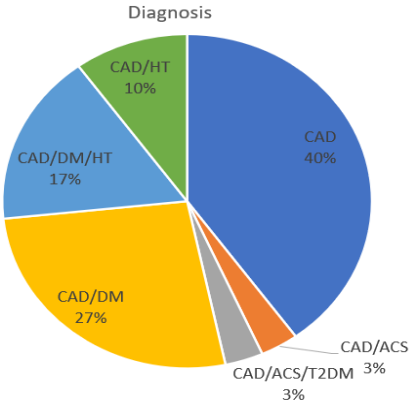

Figure 9: Diagnosis Of The Study Population

Duration Of Atorvastatin Treatment By The Study Participants

Table 10

ATORVASTATIN DURATION IN MONTHS	Frequency	Percentage
0-6	7	23.3
6-12	7	23.3
12-18	10	33.3
18-24	6	20.0
Total	30	100.0

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Table 10 shows the data of the duration of atorvastatin in the study participants. The majority of the study participants (33.3%) were taking Tab. Atorvastatin for a duration of 12 to 18 months.

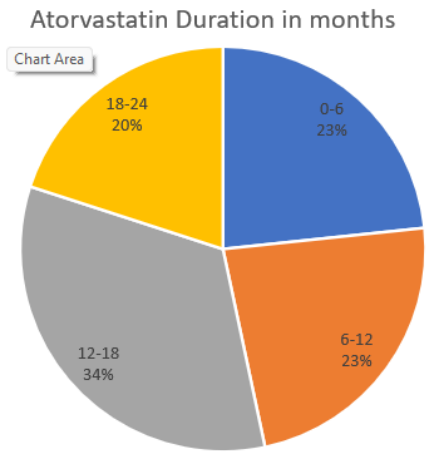

Figure 10: Atorvastatin Duration Of The Study Population

Dose Of Atorvastatin Taken By Study Participants

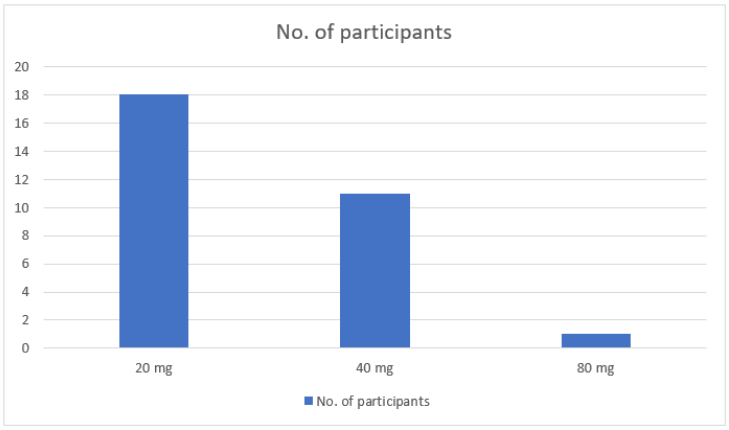

Figure 11

Table 11

Descriptive Statistics				
	Minimum	Maximum	Mean	Std. Deviation
TC	125.00	155.00	137.17	8.89
TGL	102.00	146.00	123.77	12.71
HDL	31.00	48.00	40.17	3.49
VLDL	20.00	29.00	24.73	2.59
LDL	55.00	86.00	72.27	8.40
Cholesterol/HDL ratio	2.90	4.00	3.43	0.27
TGL/HDL ratio	2.10	3.70	3.10	0.39
RBS	88.00	196.00	131.63	39.00

The table 11 shows the data of blood TC, TGL, HDL, LDL, Cholesterol/HDL ratio, TGL/HDL ratio, RBS among study participants.

- The mean blood total cholesterol level at baseline was 131.17±8.89 mg/dl
- The mean blood triglyceride level at baseline was 123.77±12.71 mg/dl

- The mean blood HDL level at baseline was 40.17±3.49 mg/dl
- The mean blood VLDL level at baseline was 24.73±2.59 mg/dl
- The mean blood Cholesterol/HDL at baseline was 3.43±0.27 mg/dl
- The mean blood TGL/HDL at baseline was 3.10±0.39 mg/dl
- The mean blood triglyceride level at baseline was 131.17±8.89 mg/dl
- The mean blood RBS level at baseline was 131.63±39.0 mg/dl mg/dl

Visual Analogue Score For Myalgia And Vitamin D3 Supplementation

Table 12

VISUAL ANALOGUE SCORE FOR MYALGIA	VAS score - Vitamin D3 Supplementation		
	BASE LINE	12 WEEK	24 WEEK
Mean	6.6	4.83	3.87
SD	0.49	0.38	0.51
p value	< 0.001 Significant		
		< 0.001 Significant	
	< 0.001 Significant		

Table 12 shows the data of mean and standard deviation of VAS score at baseline, 12 weeks, and 24 weeks.

- The mean baseline VAS score was 6.60±0.49
- The mean 12 weeks VAS score was 4.83±0.38
- The mean 24 weeks VAS score was 3.87±0.51
- VAS score was significantly higher during the baseline when compared with 12 weeks and 24 weeks.
- VAS score was significantly higher during the 12 weeks when compared with 24 weeks.
- A significant difference was obtained for VAS score in baseline and 12 weeks with a p-value of <0.001
- A significant difference was obtained for VAS score in 12 weeks and 24 weeks with a p-value of <0.001
- A significant difference was obtained for VAS score in baseline and 24 weeks with a p-value of <0.001

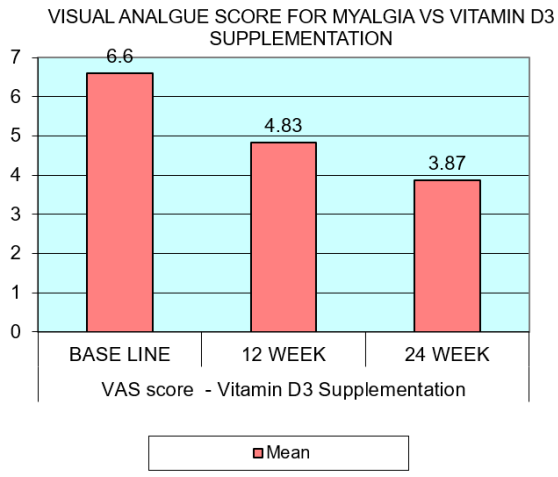

Figure 12: Vas Score – Vitamin D3 Supplementation

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Estimation Of Creatine Kinase Level In U/L With Vitamin D3 Supplementation

Table 13

CREATINE KINASE LEVEL ESTIMATION IN U/L	Mean	Std. Deviation	P-value
BASELINE	103.68	35.47	
12 WEEKS	89.28	35.35	<0.0001
BASELINE	103.68	35.47	
24 WEEKS	81.42	33.64	<0.0001

Table 13 shows the data of mean and standard deviation of creatine kinase values at baseline, 12 weeks, and 24 weeks

- The mean baseline Serum Creatine Kinase Level was 103.68±35.47 U/L
- The mean 12 week Serum Creatine Kinase Level was 89.28±35.35 U/L
- The mean 24 week Serum Creatine Kinase Level was 81.42±33.64 U/L
- A significant difference was obtained for VAS score in Baseline and 12 weeks with a p-value of <0.001
- A significant difference was obtained for VAS score in Baseline and 24 weeks with a p-value of <0.001

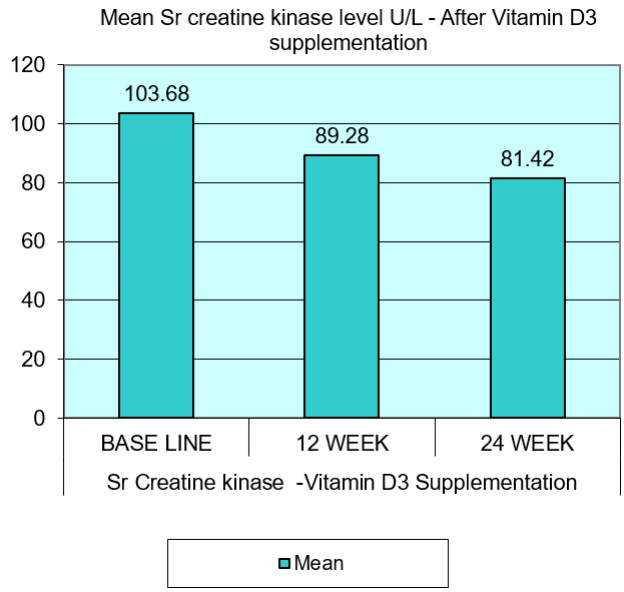

Figure 13

Correlations Between Atorvastatin Dose And Creatine Kinase Level Estimation

Table 14

Correlations				
		CK - BASELINE	CK - 12 WEEK	CK - 24 WEEK
ATORVASTATIN DOSE	Pearson Correlation	-0.205	-0.265	-0.260
	P value	0.278	0.158	0.165

No significant correlation between Atorvastatin dose and serum creatine kinase level.

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Correlation Between Atorvastatin Duration And Creatine Kinase Level Estimation

Table 15

Correlations					
			CK - BASELINE	CK - 12 WEEK	CK - 24 WEEK
Kendall's tau_b	ATORVASTATIN DURATION	Pearson Correlation	0.243	0.276	0.261
		P value	0.087	0.053	0.066

No significant correlation between atorvastatin duration and serum creatine kinase levels.

There is a significant correlation between creatine kinase and VAS score.

DISCUSSION

Muscular symptoms are the most frequently reported adverse events for statin therapy. Incidence varies from 1% to 25% from various studies. The role of serum creatine kinase levels estimation in patients on statin therapy as a diagnostic marker for myalgia is uncertain. Baseline estimation of serum creatine kinase level before initiation of statin therapy is recommended by American Heart Association Statin Advisory Panel but contradictory suggestions were issued by National Lipid Association's Muscle Expert Panel. The present study demonstrated that serum creatine kinase levels were within their reference value in patients presenting with statin-associated myalgia. This is in accordance with findings of the study reported by Smith et al. where only 0.3 % had significant elevation of creatine kinase attributed to statin therapy [11, 12]. The present study confirmed that the overall risk for CK elevation is minimal with statin use.

In our study, there is no significant correlation between atorvastatin dose and levels of creatine kinase. These results were in accordance with Baird et al [13]. but were controversial to a study done by STOMP et al. which showed the elevation of creatine kinase with high-intensity Atorvastatin therapy.

In our study there is no significant correlation between the duration of atorvastatin and creatine kinase levels is consistent with Maqsood et al that CK levels were not duration-dependent, but the extent of myalgia was duration dependent [14].

In our study, 30 participants taking statins associated with myalgia were found to have improved myalgia symptoms with vitamin D supplementation therapy. This is consistent with the study of Lee et al, Fang et al, Linde et al that serum vitamin D level is associated with statin-induced myalgia and vitamin D supplementation appear to reverse statin-induced myalgia [15-17]. Furthermore, vitamin D supplementation was safe and well-tolerated.

Ahmed et al, study postulated that the correction of vitamin D levels before statin therapy initiation may lessen the development of statin-related myalgia [18]. In contrast, Bittner et al study demonstrated that patients taking Atorvastatin did not show any relationship between Vitamin D level and myalgia incidence [19].

Draeger et al [20] used an electron microscope that documented the presence of a breakdown of the T-tubular system and subsarcolemmal rupture in skeletal muscle biopsies taken from statin-treated patients which were not present in muscle biopsies of non-treated patients.

In addition, Pfeifer et al [21] documented a decrease of ATP-dependent calcium uptake of isolated vesicles in the sarcoplasmic reticulum in an experimental study performed in muscles of vitamin D depleted rabbits. Moreover, they documented that vitamin D plays an important role in the active transportation of calcium into the sarcoplasmic reticulum. It increased the intracellular levels of ATP and phosphate increasing protein synthesis. These data suggested that vitamin D is involved in the maintenance of normal muscle physiology. This study supported that the supplementation of vitamin D can reduce muscle damage impairing physical symptoms during the treatment with statins.

Holick et al [22] documented that the administration of vitamin D3 supplementation during a fat meal and statins can improve myalgia symptoms in statin intolerance patients.

Al-Said et al [23] demonstrated reversible electromyographic changes, consistent with myopathy that resolved once vitamin D levels were improved.

Though CK levels represent biochemical markers for muscle damage, it depends on relative amounts of CK released, degree of enzyme activity of released CK, and the rate of clearance of CK from the serum [24].

As the sample size is small, our participants associated with myalgia on statins had normal CK values.

Some of the potential mechanisms that account for the effectiveness of vitamin D supplementation on statin-induced myalgia. Muscle cells have vitamin D receptors. Proximal muscle weakness, prolonged time to peak contraction and relaxation, and generalized musculoskeletal pain are associated with low levels of plasma Vitamin D levels. When the patients are supplemented with vitamin D, it may enhance the skeletal muscle function through morphological adaptations and enhanced calcium availability during cross-bridge cycling. Since Vitamin D is an inducer of CYP3A4, thereby increases the metabolism of statins, particularly atorvastatin which is primarily metabolised by CYP3A4. Vitamin D supplementation increases atorvastatin metabolism, thereby reducing myopathic side effects.

Our study results confirmed that creatine kinase levels who were taking statins associated with myalgia were statistically decreased on vitamin D3 supplementation. By logistic regression, the only significant predictor for muscle-related symptoms at the 24th-week follow-up was decreased serum creatine kinase levels. This is consistent with our hypothesis that statin-associated with myalgia was largely be resolved by vitamin D supplementation.

In the study of Chogdu et al, conducted on Wister rats, the effect of the combination of vitamin D analogue with statin and use of statin alone on CK levels and muscle fibre histology was studied. The study demonstrated that the duration of intake of vitamin D decreased the elevated CK levels and even become comparable to control [25].

The clinical spectrum of vitamin D deficiency includes myopathy and increased serum CK; normalization of CK after vitamin D treatment has been reported [26] by Ishikawa et al.

Calza et al, demonstrated that there was a statistically significant association between vitamin D deficiency and the development of myalgia or creatine kinase elevation and myalgia [27].

The following were the limitations of this study

- Study sample was collected at a single Medical College Hospital, the demographic data of the cases studied may not be a representative sample of the whole population or a particular region.
- Vitamin D levels were not estimated
- Since this study included only the patients' taking statins associated with myalgia, we cannot determine the variation in creatine kinase levels among statin patients.
- Small sample size is a major limitation of this study.
- Another major limitation of our study was that one of the endpoints was myalgia assessment by VAS score were subjective
- The mechanism(s) by which CK is cleared from the blood has not been fully elucidated, and observed serum CK levels likely reflect complex interactions associated with energy status and scale of muscle disturbance.

CONCLUSIONS

To conclude that the supplementation of vitamin d3 among patients taking statins associated with myalgia brings down their mean serum creatine kinase levels with significant improvement in myalgia. Hence, supplementation of vitamin D3 can be considered along with statins

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