DOI: https://doi.org/10.53350/pjmhs2216265

ORIGINAL ARTICLE

Vitamin D Supplementation reduces Atorvastatin induced Myopathy in Dyslipedemic patients

MARYAM NADEEM[1], SAADIA SHAHZAD ALAM[2], SYEDA MAH E NOOR ZAHRA[3], SHOAIB M DANIYAL[4], HUMA ZIA[4], MARYAM SAQIB[5], MARYAM NADEEM[6]

[1]*Senior Demonstrator, Department of Pharmacology and Therapeutics, Avicenna Medical and Dental College Lahore.*
[2]*Professor of Pharmacology, Department of Pharmacology and Therapeutics, FPGMI SKZM &DC.*
[3]*Senior demonstrator, Department of Pharmacology and Therapeutics, Akhtar Saeed Medical and Dental college Lahore.*
[4]*Assistant professor of Cardiology, SIMS/ Services Hospital Lahore,*
[5]*Demonstrator of Pharmacology, FPGMI SKZM & DC.*
[6]*Assistant professor of Pharmacology, Avicenna Medical and Dental college Lahore.*
Correspondence to Dr. Maryam Nadeem, Email: drmnadeem61@yahoo.com, cell: 0336-7444258

ABSTRACT

Background: Dyslipidemia is becoming one of the most common problems worldwide predisposing towards atherosclerotic cardiovascular events and other issues like obesity. Statins are imperative for treating dyslipidemia. However statin-intolerance is a major hurdle due to the myopathy incurred with their usage, ranging from mild aches and pains without CPK elevation to marked increase in CPK levels with myonecrosis and even death in rare cases.

Aim: Local identification of dyslipedemic patients with reduced vitamin D levels and intolerance to ≥2 statins (especially Atorvastatin), exhibiting statin induced myopathy with CPK elevation. Assessment of 3 months vitamin D therapy on myopathy and patient compliance to statins

Place and duration of study: A 13 months study conducted in Army Cardiac Center Lahore .

Methods: Upon Ethical Board Clearance (Ref No:F.39/NHRC/Admn/IRB/40)(IRB- Number: 1547) 60 dyslipidemic patients ranging from 40-70years of age, having CPK confirmed myopathy (CK levels >120micrograms/L) and intolerance to ≥2 statins (including Atorvastatin) along with hypovitaminosis D were assessed for enrollment based on strict inclusion and exclusion criteria at Army Cardiac Center Lahore.

Results: Baseline investigations including CBC, renal, liver and thyroid function tests, vit D, vit B12, hepatitis B, C, FBS, CK, CK MB and lipid profile were performed.At the end of the study at 3rd month (2ndfollowup) investigations such as 25 hydroxy vitamin D levels, presence or absence of muscular pain as symptom of myopathy and CPK with its isoenzymes CK MB levels were repeated and compared with the baseline values

Conclusion: In this study it is concluded that by replenishing vitamin D levels, Atorvastatin induced myopathy improves leading to more compliance towards the drug and resulting in improvement in lipid profile**.**

Keywords: Dyslipidemia, Vitamin D, Myopathy, Atorvastatin

INTRODUCTION

Ischemic heart disease is the leading cause of death in the world[1]. Underlying which is the atherosclerotic plaque where lipids play a major role in narrowing of arteries and reduction in blood flow through them [2]. The rupture of this plaque triggers a cascade of events such as platelet aggregation, inflammation and thrombus formation leading to abrupt closure of vessel and an acute emergency such as myocardial infarction[3]. Dyslipidemia along with other well-known risk factors such as obesity, hypertension and smoking contribute towards development of atherosclerotic disease [4].

Dyslipidemia is increased levels of total cholesterol, low-density lipoprotein, non-high-density lipoprotein, triglycerides, and reduced HDL[5, 6]which is mostly caused by high fat intake, sedentary lifestyle or hereditary reasons (Davis, 2017). Thus substantially lowering low-density lipoprotein cholesterol and treating dyslipidemia with statin therapy results in reduction of cardiovascular events[7], and produces greater benefits. Data shows that satins can cause reduction of upto 40 mg per deciliter (1 mmol per liter) in the LDL cholesterol level, and thus decreases the incidence of stroke, heart attack and revascularization by one fifth[8]. This effectiveness has resulted in making statins one of the most prescribed drugs in USA and worldwide[9].

Statins are considered amongst the safest of drugs. They are also known as hydroxyl-methyl-glutaryl-coenzyme-A (HMG-CoA) reductase inhibitors and are the keystone in preventing atherosclerotic cardiovascular diseases. These drugs are first line choice for dyslipidemia, other drugs considered areezitimide, bile acid sequestrants, fibric acid derivatives, and nicotinic acid along with dietary modifications[6]. In some cases they can cause skeletal muscle, metabolic, neurological, and other possible side effects[10].The most common among them are its muscular symptoms with or without elevated creatine kinase levels (i.e., myopathy), and occasionally, muscle breakdown resulting in myoglobin release (i.e., rhabdomyolysis), with a risk of renal failure and death[9-13]. Despite the vast variety of uses, statin intolerance is common in patients due to the above reasons.

Cause of statin induced myopathy is poorly understood with the pharmacogenetic bases effecting both pharmacokinetic and pharmacodynamic aspects**.** Statin-induced toxicity results from 40 times higher sensitivity of HMG CoA reductase inhibition leading to mevalonate synthesis inhibition and of its metabolites cholesterol, isoprenoids, and ubiquinone (coenzyme Q10[14].

Vitamin D deficiency without concomitant use of statins can cause myalgias, myositis and less likely rhabdomyolysis. Very low serum vitamin D levels result in decrease muscle function and muscle weakness[15, 16].In U.S population vit D deficiency is highly prevalent condition present among young and adults affecting 30-50% of population[17]. In our population this problem is the most undertreated and under-diagnosed because of the assumption that we people enjoy plenty of sun exposure. This nutritional disorder is affecting 53.5% of the population in Pakistan despite abundant sunshine. Problem is affecting all age groups including infants, old age and pregnant women [18]. The level 20ng/L is considered as optimum value and the levels below it are considered deficient while those above it are sufficient. These levels are affected by sunlight, dietary intake and metabolic status of an individual hence can be improved by supplementations, sun light exposure and food containing high levels of vitamin D. The supplements can be either the form of oral or parentral preparations[18].

According to many researches in different areas statin induced myalgias are predominantly found in individuals with

Received on 24-08-2021
Accepted on 11-01-2022

vitamin D deficiency and upon correction decrease in this muscular problem is observed [8, 16, 18, 19]. Many of these retrospective and two prospective studies till date[12,17] support this theory while few are against this relation[20]. But no such trial is been done in Pakistan.

The objective of the study was to find out that Vitamin D supplementation reduces Atorvastatin induced Myopathy in Dyslipedemic patients

MATERIAL AND METHODS

This study was conducted after getting approval from Ethical Committee, in Army Cardiac Center CMH Lahore. 60 dyslipidemic patients (army and civilian background) ranging from 40-70years, having CPK confirmed myopathy (CPK levels >120mcg/L),hypovitaminosis D (vit D<20ng/ml) and intolerance to ≥2 statins (including Atorvastatin) were assessed for enrollment. The patients had either stopped taking statins completely due to muscular pain or were taking them intermittently as per their own wishes resulting in failure of treatment goals. Baseline investigations including CBC, renal, liver and thyroid function tests, vit D, vit B12, hepatitis B, C, FBS, CK, CK MB and lipid profile, blood pressure and BMI were assessed. 14 patients were excluded for not matching our inclusion criteria and remaining 46 were enrolled and made to stop Atorvastatin completely for 3 weeks and given oral vitamin D supplements 50,000IUto the deficient patients (vit D level <20ng/ml) (59 patients) and 100,000IU to severely deficient patients (vit D level <10ng/ml)(7 patients). After that the supplementation was continued along with the statin i.e. Atorvastatin throughout the study duration of 3 months. The first follow up was at 3 weeks for assessing patient's compliance, improvement in symptoms and counseling was done After 3 months at 2nd follow up, only vit D status, presence or absence of muscular pain symptoms and CPK (with its isoenzyme CKMB) levels were compared with baseline. Patient's compliance towards the medicine was ensured. Weekly calls for reminder of taking vit D supplementation were made to every patient. The patients were advised to maintain the same level of food intake and physical activity as before and to report any adverse effects. If there was no improvement in the muscular symptoms after 1st follow up at 3 weeks then the patients were supposed to be excluded from the research however no drop out was seen.

Statistical analysis: Data was entered and analyzed using Statistical Package of Social Sciences latest version. Data for age, weight, BMI, FBG, lipid profile, Vit D, LFTs, RFTs, Vit B12, thyroid profile was measured at baseline, while Vit D and CK(with is isoenzyme CKMB) at baseline and 2nd follow up, and described using Mean±SD for normally distributed and median(IQR) otherwise. Pain as a symptom of myopathy was noted for each patient as present or absent and as cumulative percentage. Significance of the changes on Vit D supplementation treatment was tested using Paired t-test if normally distributed or nonparametric paired Wilcoxon test otherwise. A p-value ≤ 0.05 was considered as significant.

RESULTS

Normality of the data was assessed by Shapiro Wilk test. As data was normally distributed, paired sample t test was used to determine the mean difference in CPK and CK MB from baseline to 3months.

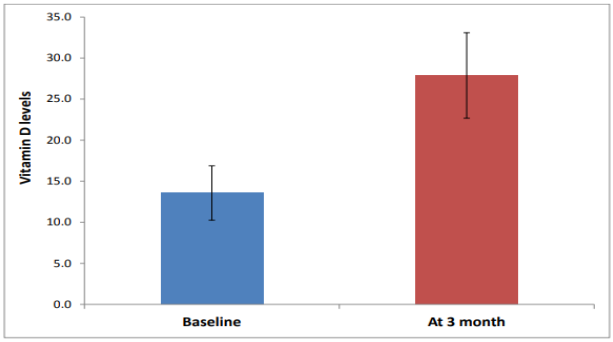
Vitamin D levels: Normality of the data was assessed by Shapiro Wilk test. As data was non-normally distributed, Wilcoxon signed ranks test was used to determine the mean difference in Vitamin D levels from baseline to 3months. Comparison by Wilcoxon signed ranks test revealed that Vitamin D levels significantly increased after 3month of treatment.

Table 1: Change in Vitamin D levels at 3months from the baseline (n=46)

Variable	Baseline Mean ± SD	After 3 month Mean ± SD	Wilcoxon signed ranks test p-value
Vitamin D levels	13.6 ± 3.3	27.9 ± 5.2	< 0.001*

*significant

Figure 1: Change in CK levels at 3month from the baseline



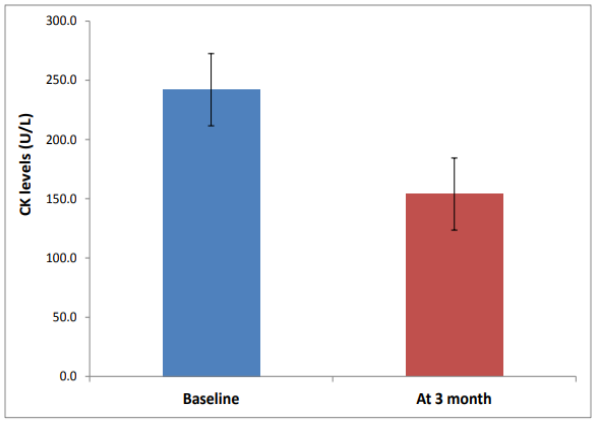
Comparison by paired t-test revealed that CK levels significantly decreased after 3month of treatment.

Table 2: Change in CK levels at 3month from the baseline (n=46)

Variable	Baseline Mean ± SD	After 3 month Mean ± SD	Paired t-test p-value
CK levels (U/L)	242.0 ± 30.5	154.0 ± 30.4	< 0.001*

*significant

Figure 2: Change in CK levels at 3month from the baseline



DISCUSSION

One in 4 middle-aged adults in Pakistan has prevalent yet preventable CAD. Risks are uniformly high in the young and in women. Concerted efforts are needed to prevent dyslipidemia which is the major cause compounded by dietary and lifestyle factors[20]. Statins are key drugs that can cause reduction of upto

40 mg per deciliter (1 mmol per liter) in the LDL cholesterol level, and thus decreases the incidence of stroke, heart attack and revascularization by one fifth [8].

Statins are considered amongst the safest of drugs. Although they can cause myopathy, affecting 1 in 1000 to 1 in 10, 000 people on standard statin doses [21].Myopathy can be with or without elevated creatine kinase levels, and can occasionally cause muscle breakdown resulting in myoglobin release (i.e., rhabdomyolysis), with a risk of renal failure and death[10, 12, 13, 21911]. Vitamin D deficiency without concomitant use of statins can cause myalgias, myositis and less likely rhabdomyolysis. Very low serum vitamin D levels result in decrease muscle function and muscle weakness [15, 16]. It is observed that some patients with myopathy perceived to be statin induced might be due to vit D deficiency and upon correction of this vitamin deficiency the muscular symptoms improve and may disappear completely.

Due to vit D involvement in statin metabolism Myopathy was found to be severer in vitamin D deficient individuals with beneficial response upon its supplementation. Therefore studies have been conducted in US and most were just about comparing the vit D levels in statin induced myalgic patients taking combination of statins and not Atorvastatin as sole drug.

Our population varies from them in our cytochromic genome and vit D levels are also found to be lower amongst us.Yet no indigenous clinical trial has been conducted despite our genetic, geographic and environmental uniqueness.

Amongst the statins atorvastatin is prescribed most commonly in our settings as it is considered relatively safer making it our research drug.

Therefore in this study we assessed if correction of hypovitaminosis D through supplementation results in decrease in severity of previously intolerant statin induced myalgia in the army health services setup of Lahore.

Statins lowers the cholesterol, LDL and trigleceride levels and increase HDL levels by inhibiting the 3-hydroxy-3-methylglutaryl coenzyme A (HMG–CoA) reductase. Our results pointed towards the importance of vitamin D therapy in improving patients compliance to statins making them more tolerable due to reduction in their previously experienced myalgias ultimately leading to correction of lipid profile. This correction in lipid profile leads to lower chances of developing associated complication like coronary heart diseases as proved by various studies.

Few western studies concur with our findings. The first being a case report in 2010 by David S. H.Bell the levels of LDL, triglycerides and HDL improved from 189mg/dl, 158mg/dl and 58mg/dl to 98mg/dl, 122mg/dl and 59mg/dl respectively after correcting her vit D levels from 17ng/ml to 42ng/ml by giving oral supplementation for 3 months resulting in development of compliance towards rosuvastatin.

Charles J Glueck and Brandon Conrad in 2013 found median LDL cholesterol to decrease from 146 to 95 mg/dl (p value >0.001) after giving vit D supplementation to previously deficient individuals leading to develop statin tolerance.

We found the baseline vit D levels to be 13.6 ± 3.3ng/ml and that of 3 months follow-up to be 27.9 ± 5.2ng/ml. The p-value being < 0.001. Vitamin D supplementation given in doses of 50000IU and 100000IU according to the baseline levels improved the amount of 25 hydroxy vitamin D levels in our patients.

Our results concurred with Karin Amrein et al in 2011 with a few differences. Their double blind placebo controlled study showed drastic improvement in vit D levels in patients with hypovitaminosis D with only 2 days of high dose oral vit D administration whereas ours was a 3 month interventional study. In this study it was observed observed that mean serum 25(OH) D levels to increase upto 25 ng/ml (range 1-47 ng/ml) in the group taking oral high dose supplement (540,000IU). The highest level of 25(OH) D reached was 64ng/ml,

Valentine Milazzo and colleagues wrote in World Journal of Cardiology in 2017 that low vit D level itself is strongly related to development of myocardial infarction. The rationale given by him was that firstly there is link between both the presence of receptors for vit D at myocardium and vascular cells. Secondly there is a role of vit D in developing risk factors of ischeamic heart disease such as diabetes, hypertension and metabolic syndrome. Thirdly the increase in incidence of hypovitaminosis D and myocardial infarction during winter is noted with decrease in sunlight and distance from the equator.

In our study the markers for assessing myalgias which was CK improved by showing a significant decline (p value=0.001) of 37.6 % value from 242.0 ± 30.5 U/L at baseline to 154.0 ± 30.4 U/L at 3 months. To specifically determine biochemically the source of pain perceived to be myalgic by the patients from cardiac pain, the isoenzyme of CK, CK MB (myocardial band) levels were measured. The criteria for it is that CK MB levels less than 10% of the total CK levels are muscular whereas more are cardiac. According to lab test online (March 2021) if ratio of CK-MB to total CK is more than 2.5-3 than the cause of pain would said to be from heart otherwise it would be musculoskeletal. We found our patients to have CK MB levels less than 10% of total CK both at baseline 20.5 ± 4.2 U/L and at 3 months12.5 ± 3.6 U/L confirming the source of pain to be muscular. Importantly a 39% decline of CK MB was noted from baseline which confirmed improvement in myopathy at the cellular level. Simultaneously 100% symptomatic improvement of muscular pain was felt by all 46 patients.

In totality our local population showed marked improvement in CK levels with symptomatic reduction in myalgia and improving vit D levels through oral vit D supplementations for 3 months. Hence making statin (atorvastatin) usage more tolerable to these patients.

Vitamin D is an inducer of CYP3A4 and CYP2C9, it can be expected that it will help in the metabolism of certain statins and reduce their toxic side effects. Thus low vitamin D levels might reduce CYP3A4 activity, with resultant increase in the serum statin levels and subsequent statin myotoxicity[22].

For comparison we found a contrasting local study by Dr Ayla K. et al in 2014 at Shifa International Hospital in which no association was noted between low vitamin D levels and statin induced myopathy. Non significant difference was found between vit D levels of 24 patients with statin induced myalgias 17.98 ± 12.07 versus 18.99 ± 15.2 mean vit D levels of 25 patients with no statin induced myalgias.

Concurring data was noted from a retrospective study by Krista D et al. in 2016 conducted on 105 patients showing 79% of patients with vit D deficiency (vit D= 32ng/ml) to have statin induced myopathy (p value= 0.037).

A prospective study by Khavznikov et al. 2015 showed that upon correction of vit D levels myopathic patients were symptomatically improved. The percentage of improved patients was 88%, 91% and 95% after 6, 12 and 24 months respectively.

Travis Morioka et al. 2015 reported patients with vit D levels <15ng/ml to have more musculoskeletal pain after taking statins (adjusted odds ratio,1.90; 95% CI, 1.18-3.05) as compared to those with vit D >15ng/ml (aOR, 0.91; 95% CI, 0.71-1.16).

All the above studies emphasized on gathering newer data in the context of vit D and its relation to statin induced CPK deranged myopathy in different populations because of the pharmacogenetic variations worldwide. Our study is a step in the right direction.

CONCLUSION

Our unique local study conducted on the Pakistani population found that dose dependant oral vitamin D supplementation for three months in hyperlipidemic patients with statin intolerance improved statin (Atorvastatin) induced myopathy. Leading to enhanced statin compliance and improvement in lipid profile and expected health benefits.

Limitations: It was not a double blind study in a proper controlled environment with proper monitoring. And patients not showing muscular symptoms improvement could not continue the research.
Conflict of interest: Nil

REFERENCES

1. Pagidipati NJ, Gaziano TA. Estimating deaths from cardiovascular disease: a review of global methodologies of mortality measurement. Circulation 2013; 127(6): 749-56.
2. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002; 105(9): 1135-43.
3. Kontush A, Chapman MJ. Functionally defective high-density lipoprotein: a new therapeutic target at the crossroads of dyslipidemia, inflammation, and atherosclerosis. Pharmacological reviews 2006; 58(3): 342-74.
4. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. Guidelines: Editor's choice: 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European heart journal 2016; 37(29): 2315.
5. Nielsen TRH, Lausten-Thomsen U, Fonvig CE, Bøjsøe C, Pedersen L, Bratholm PS, et al. Dyslipidemia and reference values for fasting plasma lipid concentrations in Danish/North-European White children and adolescents. BMC pediatrics 2017; 17(1): 1-11.
6. Mahamuni SP, Khose RD, Menaa F, Badole SL. Therapeutic approaches to drug targets in hyperlipidemia. BioMedicine 2012; 2(4): 137-46.
7. Egan A, Colman E. Weighing the benefits of high-dose simvastatin against the risk of myopathy. N Engl J Med 2011; 365(4): 285-7.
8. Palamaner Subash Shantha G, Ramos J, Thomas-Hemak L, Pancholy SB. Association of vitamin D and incident statin induced myalgia—a retrospective cohort study. PLoS One 2014; 9(2): e88877.
9. Parker BA, Thompson PD. Effect of statins on skeletal muscle: exercise, myopathy, and muscle outcomes. Exercise and sport sciences reviews 2012; 40(4): 188.
10. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. Jama 2003; 289(13): 1681-90.
11. Bell D. Resolution of statin-induced myalgias by correcting vitamin D deficiency. South Med J 2010; 103(7): 690-2.
12. Khayznikov M, Hemachrandra K, Pandit R, Kumar A, Wang P, Glueck CJ. Statin intolerance because of myalgia, myositis, myopathy, or myonecrosis can in most cases be safely resolved by vitamin D supplementation. North American journal of medical sciences 2015; 7(3): 86.
13. Zubair AK, Ahmad IN. Association of vitamin D with statin induced myalgia. Pakistan Journal of Neurological Sciences (PJNS) 2015; 10(2): 19-22.
14. Vladutiu GD. Genetic predisposition to statin myopathy. Current opinion in rheumatology 2008; 20(6): 648-55.
15. Simpson R, Thomas G, Arnold A. Identification of 1, 25-dihydroxyvitamin D3 receptors and activities in muscle. Journal of biological chemistry 1985; 260(15): 8882-91.
16. Morioka TY, Lee AJ, Bertisch S, Buettner C. Vitamin D status modifies the association between statin use and musculoskeletal pain: a population based study. Atherosclerosis 2015; 238(1): 77-82.
17. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency: an important, common, and easily treatable cardiovascular risk factor? Journal of the American College of Cardiology 2008; 52(24): 1949-56.
18. Akhtar RR, Khan J, Zahid T, Ahmed R. VITAMIN-D LEVELS AND LOW BACK PAIN. The Professional Medical Journal 2018; 25(04): 615-9.
19. Shinchuk L, Holick MF. Vitamin D and rehabilitation: improving functional outcomes. Nutrition in Clinical Practice 2007; 22(3): 297-304.
20. Riphagen IJ, van der Veer E, Muskiet FA, DeJongste MJ. Myopathy during statin therapy in the daily practice of an outpatient cardiology clinic: prevalence, predictors and relation with vitamin D. Current medical research and opinion 2012; 28(7): 1247-52.
21. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. Journal of the American College of Cardiology 2016; 67(20): 2395-410.
22. Bhatt RD, Pradhan N, Gurung R, Risal P. Hypovitaminosis D in Healthy Health Care Professionals: A Real Deficiency or Necessity of New Reference Value for Specific Population? Journal of Lumbini Medical College 2018; 6(1): 1-5.