Original Article

Early Effects of Atorvastatin on Vitamin D and Parathyroid Hormone Serum Levels Following Acute Myocardial Infarction

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ABSTRACT

Objective: High Vitamin D serum level after acute myocardial infarction (aMI) has shown to increase cardiac reconstruction by increasing cell survival and enhancing angiogenesis. Atorvastatin has a well-defined role in both primary and secondary prevention of cardiovascular diseases. It is suggested that this effect may partly be attributable to raising 25-hydroxyvitamin D concentrations. The aim of this study was to evaluate atorvastatin effects on Vitamin D and parathyroid hormone (PTH) levels early after aMI. **Methods:** All patients admitted with aMI in Imam Reza Hospital, Mashhad, Iran, from July 2014 to March 2015, were included in this pre- and postintervention study. Serum levels of Vitamin D and PTH were measured on admission and the 3rd day after administration of atorvastatin 80 mg/day. **Findings:** A total of 69 post-aMI patients (47 males and 22 females) were enrolled in this study. Serum levels of Vitamin D and PTH were significantly higher (23.52 ng/ml and 46.04 pg/ml, respectively) after 72 h of atorvastatin therapy compared to the baseline (19.66 ng/ml and 31.19 pg/ml, respectively) (P = 0.004 and 0.002, respectively). **Conclusion:** The early post-aMI beneficial effects of atorvastatin can be attributed to increased serum Vitamin D level; however, atorvastatin cannot significantly decrease serum PTH level after aMI. Further studies are needed to elucidate the clinical effect of atorvastatin.

Keywords: *Acute myocardial infarction, Atorvastatin, parathyroid hormone, Vitamin D*

Introduction

Acute myocardial infarction (aMI) continues to be a major public health problem in the world. Early myocardial remodeling occurs within 72 h after aMI.[1] Low serum concentrations of 25-hydroxyvitamin D (25OHD)[2] and elevated parathyroid hormone (PTH) levels have been reported in aMI patients.[2,3] A probable relationship has been proposed between low Vitamin D serum level and early myocardial remodeling.[4] Although the association between the impaired Vitamin D – PTH axis and early myocardial remodeling has not been evaluated yet, PTH exerts a direct hypertrophic effect on the cardiomyocytes.[5]

Thus, investigation of the relationship between altered Vitamin D – PTH status immediately after aMI and the severity of myocardial damage seems reasonable.

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There are controversial reports regarding the reciprocal effects of statins and Vitamin D in various conditions. While some studies indicate that atorvastatin and rosuvastatin treatments elevate 25OHD levels,[6-8] other reports infer that fluvastatin and atorvastatin have no effects of Vitamin D levels.[9] Moreover, Vitamin D levels have been reported to affect the efficacy of statins.[10,11] Statins have shown cardioprotective effects and increased post-MI survival through several mechanisms regardless of their cholesterol-lowering property.[12] In-hospital initiation of statin therapy has been recommended to benefit from early post-MI effects of statins, improve clinical outcomes, and also reduce 1-year mortality.[13,14]

Atorvastatin is one of the most widely prescribed statins with a well-defined role in both primary and secondary prevention of cardiovascular diseases, being referred to as pleiotropic effects.[15] The protective role is mostly related to its anti-inflammatory effect, as different inflammatory processes are involved in post-MI myocardial damage.[16] Atorvastatin significantly suppresses the elevated levels of cardiac troponin-I, C-reactive protein, tumor necrosis factor-1,[17,18] and plasminogen activator inhibitor-1[19] while causes a significant increase in nitric oxide (NO) production by increasing endothelial NO synthase mRNA stability.[20] However, numerous investigations have found that the pleiotropic effects of atorvastatin may be attributable in part to raising 25OHD concentrations.[7,21,22]

Increasing evidence shows high prevalence of Vitamin D deficiency in acute MI patients.[3] On the other hand, Vitamin D signaling itself plays an essential role in cardioprotection after MI through anti-inflammatory, antifibrotic, and antiapoptotic properties.[23-25]

The aim of this study was to evaluate the probable effects of early administration of atorvastatin on Vitamin D and PTH serum levels in post-MI patients.

Methods

All patients with acute MI were enrolled in this pre- and postintervention (quasi-experimental) study conducted between July 2014 and March 2015 at the Department of Cardiology, Imam Reza Hospital, Mashhad University of Medical Sciences [Figure 1]. To detect an intragroup difference of six points in Vitamin D level from baseline to follow-up with a statistical power of 80%, a Type I error risk of 5%, and an estimated standard deviation (SD) of 6.5%, a total of 78 patients were estimated to be needed for enrollment in the study. The inclusion criteria consisted of confirmation of the diagnosis of aMI based on medical history, physical examination, clinical presentation, and laboratory data.

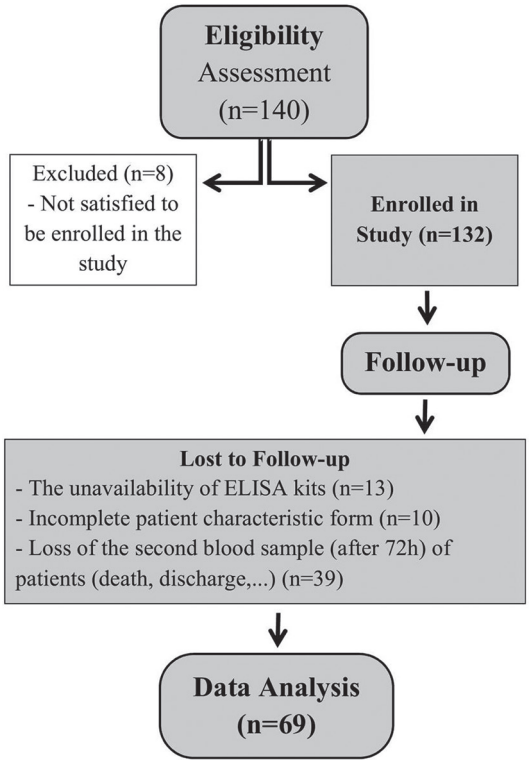

Figure 1: Flow diagram of the study design

Patients with a history of atorvastatin and Vitamin D supplements, antiepileptics, corticosteroids, lithium, isoniazid, and rifampin use before admission, renal dysfunction (GFR <50 ml/min), hepatic failure (serum transaminase levels >2–3 times higher than the normal upper limit), heart failure, osteoarticular disorders, active infection, calcium and phosphorus metabolic disorders, and malignancy were excluded from the study.

A questionnaire containing demographic and laboratory data as well as drug, medical, and family history of cardiovascular diseases was completed for all patients. All included patients declared fair sunlight exposure and dietary regimen.

The population sample was categorized into three groups according to serum Vitamin D level: Vitamin D deficiency = 25(OH)D ≤15 ng/ml (n = 24 participants); Vitamin D insufficiency = 15 <25(OH)D ≤30 ng/ml (n = 36); and Vitamin D sufficiency = 25(OH)D >30 ng/ml (n = 9).

Atorvastatin 80 mg daily in two divided doses was prescribed for all patients after the diagnosis of aMI.

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences (#1686). All participants signed written consent forms.

Mid- and long-term (3, 8, and 12 months) changes in serum Vitamin D levels have already been reported

after statin administration; however, short-term effects of statins have not been studied yet.[6-8,26] Moreover, patients with acute MI are usually hospitalized in the cardiac/coronary care unit for <5 days.[27,28] Hence, in this study, venous blood samples were collected from patients on admission and the 3rd day of hospitalization.[29] The plasma fractions were isolated and stored at −70°C until analysis. Vitamin D and PTH serum levels were measured using an ELISA kit (Calbiochem, UK). Each assay was calibrated using a standard curve according to the manufacturer's instructions. Based on kit brochure, the normal range of serum PTH in healthy population was 13–66 pg/mL. Routine biochemical measurements such as plasma glucose, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, serum calcium and phosphorus, and serum electrolyte were carried out through routine laboratory methods on admission, the next day (as fasting blood tests), and whenever needed.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM corp., Armonk, New York, USA). The quantitative variables were presented as mean ± SD. All numeric variables were tested for normality of distribution by the Kolmogorov–Smirnov test. Paired sample *t*-test was used to compare the changes between the baseline and the 3rd-day Vitamin D and PTH serum concentrations. When necessary, Wilcoxon rank-sum test was used for nonnormally-distributed data. Statistical significance was set at $P < 0.05$. One-way analysis of variances was used to compare the mean differences in age and body mass index (BMI) between Vitamin D status subgroups (Vitamin D deficiency: 25(OH)D3 ≤15 ng/ml; Vitamin D insufficiency: 15 <25(OH)D3 ≤30 ng/ml; and Vitamin D sufficiency: 25(OH)D3 >30 ng/ml). The correlations between the changes in Vitamin D and PTH serum levels were assessed by Pearson's test.

Results

A total of 69 participants (47 men and 22 women) from 140 evaluated patients were enrolled in the study during 8 months [Figure 1]. The average age and BMI of the patients were 61.86 ± 13.3 years and 25.08 ± 3.60 kg/m^2, respectively. The patients' baseline characteristics are summarized in Table 1. No significant difference was found in demographic data and Vitamin D status between the two time points. Majority of the patients (65.2%) had Vitamin D insufficiency (52.2%) or deficiency (13%). Subgroup analysis based on Vitamin D status revealed that there was a significant difference in gender distribution in three groups of patients ($P = 0.007$) [Figure 2]. However, no significant difference was found in age ($P = 0.244$) and BMI ($P = 0.151$) between different Vitamin D status subgroups.

Table 1: Patient's baseline demographic, clinical, and paraclinical data

Variables	*n* (%)/mean±SD
Age (year)	61.86±13.3
Gender (%)	
Male	47 (68.1)
Female	22 (31.9)
BMI (kg/m^2)	25.08±3.60
MI type (%)	
STEMI	54 (88.5)
Non-STEMI	7 (11.5)
Hypertension	30 (43.5)
Diabetes (%)	
Type I	6 (8.7)
Type II	11 (15.9)
IHD	16 (23.2)
Smoking (%)	
Yes	19 (27.5)
No	45 (65.2)
Former	5 (7.2)
FH for cardiovascular disease	35 (50.7)
Vitamin D serum level (nmol/L)	19.65±12.62
PTH serum level (pmol/L)	31.19±18.79
CPK-MB (IU/L)	93.06±93.76
Calcium (mg/dl)	8.77±0.57
Phosphorus (mg/dl)	3.83±0.68

STEMI=ST elevation MI, MI=Myocardial infarction, IHD=Ischemic heart disease, FH=Family history, PTH=Parathyroid hormone, CPK-MB=Creatine phosphokinase MB, SD=Standard deviation, BMI=Body mass index

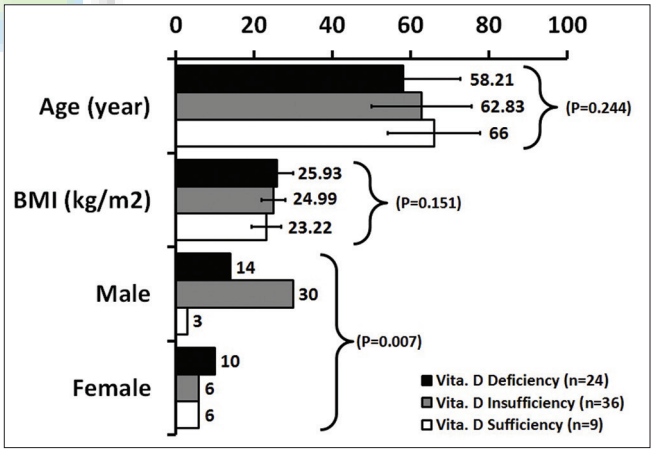

Figure 2: Subgroup analysis of age, body mass index, and sex based on Vitamin D status on admission (Vitamin D deficiency: 25(OH)D3 ≤15 ng/ml; Vitamin D insufficiency: 15< 25(OH)D3 ≤30 ng/ml; and Vitamin D sufficiency: 25(OH)D3 >30 ng/ml). 25(OH)D3 = 25-hydroxyvitamin D

The mean serum levels of Vitamin D and PTH increased significantly at the 3rd day of admission in comparison with the baseline ($P = 0.004$ and $P = 0.002$, respectively) [Figure 3].

Subgroup analysis based on Vitamin D status showed elevated serum Vitamin D levels in all three subgroups (Deficient, Insufficient, and Sufficient). Furthermore, the PTH level was increased in both Vitamin D-deficient and insufficient subgroups; however, PTH level showed a nonsignificant drop in patients with normal Vitamin D levels [Figure 4].

Considering the normal PTH range (10–65 pg/mL), none of the participants had subnormal (PTH <10 pg/mL), 64 had normal (10≤ PTH ≤65 pg/mL), and 5 had supranormal PTH (PTH >65 pg/mL) on admission time; however, 3 days after Vitamin D administration, the number of patients with normal PTH level decreased to 53 while those with supranormal PTH increased to 16 patients [Figure 5].

Changes in PTH levels were significantly inversely correlated with the changes in Vitamin D levels from baseline ($r = -0.276$ and $P = 0.021$).

Discussion

In parallel with low levels of Vitamin D, the potential role of elevated levels of PTH in the development of post-MI cardiac remodeling has been well studied.[30] According to the current available guidelines, starting atorvastatin is one of the earliest recommended therapies for acute MI, owing to its pleiotropic effects.[31,32] Long-term effects of atorvastatin administration on Vitamin D level have been defined in previous studies.[7,9,11,21,22] The mechanism by which atorvastatin increases Vitamin D levels is attributed to inhibition of 3-hydroxy-3 methylglutaryl coenzyme A reductase.[7,11] What is less clear is that whether statins provide short-term benefit for aMI patients when administered immediately after acute MI, in part through depleting PTH and raising Vitamin D concentrations.

To the best of our knowledge, no study has investigated this association. In this study, we found that the early treatment with atorvastatin 80 mg daily resulted in a significant increase in serum 25OHD concentration that was independent of the lipid-lowering effect of atorvastatin.

As early administration of atorvastatin is recommended in patients with acute MI, we were ethically limited to have a control group without atorvastatin administration. Moreover, according to the guidelines, only one recommended dose of atorvastatin (80 mg daily) could be administered and lack of various doses can be the second limitation of the study. Limited number of patients and short follow-up time can also be considered as limitations in the current study. A significant number of participants were also missed due to difficulty in obtaining the second blood sample after 72 h.

The current results are in concordance with the previous studies[7,8,21] as, based on our findings, patients with higher Vitamin D levels had nominally lower creatine phosphokinase-total ($P = 0.282$), presenting reduced tissue damage in this group. An increase in 25OHD concentrations directly in response to atorvastatin therapy, in correlation with decline in cardiac enzyme had previously been reported.[8] It is demonstrated that elevated serum PTH level is an independent factor in myocardial injury and all-cause mortality in post-MI patients.[33,34] In the current study, atorvastatin did not reverse the increasing of PTH level after acute MI in Vitamin D-deficient/insufficient patients but caused a nonsignificant drop in PTH in Vitamin D-sufficient

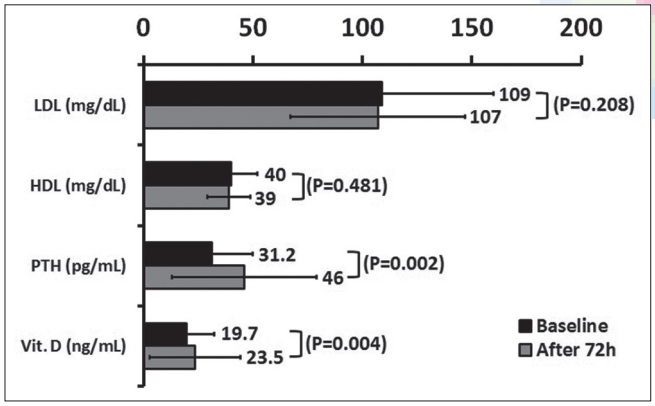

Figure 3: Comparison between the serum levels of low-density lipoprotein, high-density lipoprotein, Vitamin D, and parathyroid hormone on admission and day 3

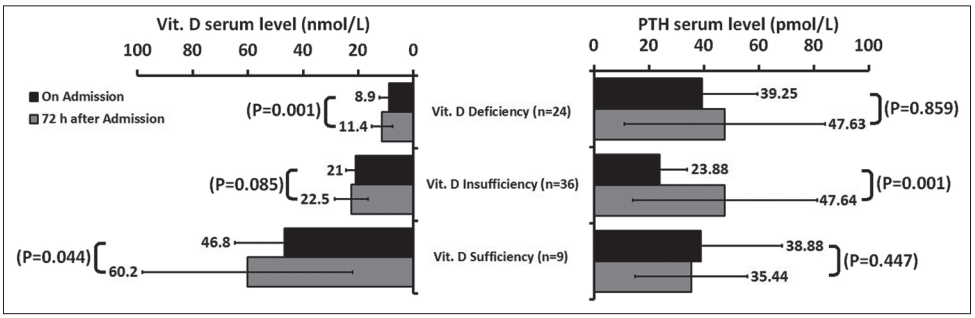

Figure 4: Subgroup analysis of serum Vitamin D and parathyroid hormone level based on initial Vitamin D status

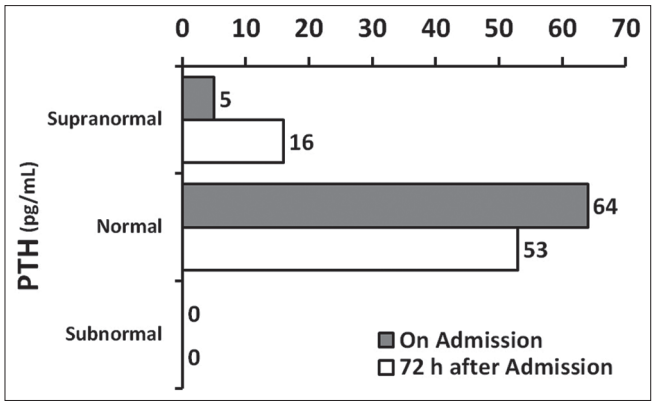

Figure 5: Subgroup analysis of parathyroid hormone level on admission and 3 days later

patients. It has been proposed that the ability of atorvastatin 80 mg daily might not be enough to reduce serum PTH level; however, it seems that the modifying effect of atorvastatin on serum PTH level might be depending on Vitamin D status. Studies with bigger populations, proper control groups, and varying doses of atorvastatin are required for the evaluation of this beneficial effect.

Furthermore, low concentrations of 25OHD in the present study were associated with high PTH levels. Since the risk of cardiovascular disease in people with Vitamin D deficiency is almost four times higher than those with normal levels,[35] adequate Vitamin D supplementation may be contributing to the prevention of early remodeling after aMI.[4] Khalili *et al*. found that administration of Vitamin D significantly decreased the matrix metallopeptidase-9 level, the early biomarkers of myocardial remodeling, in the first 72 h after aMI.[4]

Our findings revealed that early atorvastatin therapy showed marked elevation of serum Vitamin D level following acute MI; however, PTH level had controversial fluctuations from the baseline depending on patients' Vitamin D serum concentrations. Further experimental and clinical studies are necessary to verify the probable effect of atorvastatin on serum PTH level and its correlation with Vitamin D level, define the target range of Vitamin D level for prevention of post-MI complications, and clarify the ability of atorvastatin in increasing Vitamin D level for the prevention of post-MI early remodeling.

Authors' Contribution

Batool Zarei contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. Maryam Mousavi contributed in the drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. Saeideh Mehdizadeh contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. Hassan Mehrad-Majd contributed in data analysis, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. Maryam Zarif contributed in conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. Zahra Erfanian contributed in conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. Ali Moradi contributed in the conception of the work, drafting and revising the draft, data analysis, approval of the final version of the manuscript, and agreed for all aspects of the work.

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Conflicts of interest

There are no conflicts of interest.

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