World Heart Journal
Volume 11, Issue 1

ISSN: 1556-4002

Does Vitamin D3 Supplementation Affect the Outcome of Patients with Acute ST Segment Elevation Myocardial Infarction?

Mohammad A. Al Hussein[1], Najah R. Hadi[1,*], Rabab A Salman[2], Anwer S. AlZurfi[1], Hameed K. Shaalan[1], and Hayder A. Al-Aubaidy[3]

[1]College of Medicine, University of Kufa, Iraq
[2]Al Hussein Pediatrics Hospital, Diwaniyah Health Authority, Iraq
[3]School of Life Sciences, La Trobe University, Bundoora, Australia

Abstract

Background: Acute Myocardial Infarction (AMI) is one of the major causes of mortality and morbidity. Vitamin D deficiency plays an important role in pathophysiology of CAD, including atherosclerosis and endothelial dysfunction.

Objectives: This study aims to highlight the short-term effects of vitamin D3 supplementation on inflammation levels in hospitalized patients with acute ST-segment elevation myocardial infarction (STEMI).

Study group: Forty-four patients with clinical diagnosis of STEMI were included in this study.

Methods: Participants were randomized into two groups: Group I (intervention Group) received the standard treatment for AMI plus vitamin D3 5000 IU/day for 5 days. Group II (Control Group) received the standard treatment with no vitamin D3 supplementation. After taking history, performing clinical examination and electrocardiography, venous blood samples were taken at two intervals: Time zero (during hospital admission), and after 5 days follow-up for the measurement of *25-hydroxy* vitamin *D* and selected inflammatory markers (troponin I, high sensitivity C-reactive protein, Interleukin-6) and WBC counts.

Results: There was a significant increase in the level of 25-hydroxy vitamin D in the Intervention Group (30.1 ± 13.2 ng/ml) after 5 days of its supplementation, as compared to the baseline (24.2 ± 13.3 ng/ml), $P<0.001$. However, this was not associated with a significant reduction in the degree of inflammation, except for the levels of interleukin-6 (baseline level was 27.45 ± 9.85 pg/ml, and post-treatment level was 21.52 ± 8.49 pg/ml, $P<0.001$. Such differences were not found in the Control Group.

Conclusion: Vitamin D3 supplementation had no significant effects on the outcomes of the acute inflammatory response in patients with acute STEMI, in spite of the significant inverse correlation between baseline vitamin D levels and interlukin-6 levels among all participants of this study.

Keywords: acute ST-segment elevation myocardial infarction, vitamin D, acute inflammation, interleukin-6, cardiac troponin-i, interleukin-10, hsCRP, WBC

* Corresponding Author's E-mail: drnajahhadi@yahoo.com

Introduction

Acute Myocardial Infarction (AMI) is one of the major causes of mortality and morbidity among populations worldwide [1]. The most common cause is coronary artery disease (CAD) with erosion or rupture of the plaque partial or complete arterial occlusion [1]. The early mortality rate of AMI was about 30%; more than 50% of these deaths occur before the patient reaches the hospital. Although the mortality rate after hospital admission of AMI has decreased to about 30% over the last decades, nearly 0.04% of the patients who survive after initial hospitalization die in the first 12 months post-AMI [2]. In the contemporary era, the in-hospital mortality rate following AMI decreased to 10% and up to 25% patients die within the first year.

Inflammation is an important key in all stages of atherosclerosis, from synthesis of fatty streak, plaque rupture, and thrombus formation causing vascular obstruction [3]. The progressive development of an atherosclerotic plaque and the local vascular events that surround an AMI can stimulate acute phase reactants and cytokines [4]. These inflammatory mediators contribute to plaque instability; thus, inflammatory markers may be used as athero-thrombotic risk predictors, such as rupture or erosion of unstable plaques, platelet activation and thrombus formation (occlusive or nonocclusive) [6].

Various studies showed that high-sensitive CRP (hsCRP) is a strong predictor for occurrence, recurrence and prognosis of acute myocardial infarction [6, 7]. It had been suggested that high level of hsCRP is an accurate indicator for vascular endothelium injury and prognosis [7]. Interleukin-6 (IL-6) may reflect the size, prognosis and extension of myocardial infarction [7, 8]. It plays a key role in atherosclerosis [8] and plays a role in the reperfusion injury, healing processes and remodeling following a heart attack [9].

Vitamin D deficiency plays an important role in the pathophysiology of CAD, including atherosclerosis and endothelial dysfunction [10], as its vasculo-protective effect, mediated by an increased production of nitric oxide, inhibits the formation of foam cells from macrophages, or decreases the expression of adhesion molecules in endothelial cells [11]. Some clinical trials showed the beneficial effects of vitamin D supplementation in patients with very low 25-hydroxy vitamin D [25(OH) D] levels [12], while other randomized clinical trials could not demonstrate a significant association between vitamin D supplementation and reduction of cardiovascular risk factors [13]. However, any favorable effects of vitamin D on cardiovascular outcomes and on inflammatory biomarkers are still being debated.

The aim of this study was to observe the short-term effects of vitamin D3 supplementation on the levels of the inflammatory markers in hospitalized patients with acute ST-segment elevation myocardial infarction.

Methods

A randomized controlled trial was conducted between February 2014 and December 2016 at Al Sader Medical City, in Al-Najaf Al-Ashraf governorate, Iraq. The study was carefully reviewed and approved by the Human Research Ethics Committee, Faculty of Medicine, University of Kufa. Informed consents were obtained from all participants before allowing them to be involved in the study.

Inclusion criteria included participants who were clinically diagnosed with ST-segment elevation myocardial infarction (STEMI) according to the WHO criteria (Ischemic symptom, ST elevation on ECG, and raised levels of cardiac enzymes) [14].

The exclusion criteria included the following: patients with concurrent inflammatory disease; malignancy; malabsorption diseases; pregnant and lactating women; liver disease; renal disease, patients with hypocalcemia or hypercalcemia; patients with peripheral and ischemic vascular disease; previous history of CAD; complicated STEMI at presentation; contraindication to thrombolysis; patients currently on medications that might interfere with vitamin D metabolism, such as steroids, *phenytoin and* digoxin, and current use of vitamin D.

A total of forty-four patients with a clinical diagnosis of STEMI were included in this study. Theywere randomized into two study groups: Group I (Intervention Group) included 22 patients who received vitamin D 5000 IU/day for 5 days in addition to the traditional treatment of STEMI. Group II (Control Group) included 22 patients who received

the traditional treatment of STEMI with no Vitamin D supplementation.

Detailed medical histories, physical examinations and electrocardiography were performed to confirm the diagnosis of STEMI and for assessment of eligibility in the light of the inclusion and exclusion criteria. Ten milliliters of venous blood were drawn at admission, prior to vitamin D3 supplementation, and after 5 days of vitamin D3 supplementation, for the measurements of human serum 25 (OH) D, troponin, hsCRP and IL-6 levels, using specific enzyme-linked immunosorbent assay kits.

Statistical Analysis of Data

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 21, USA. Numerical data were expressed as mean, standard deviation, median and inter-quartile range, whereas categorical data were expressed as number and percentages. Results were considered significant at $p \leq 0.05$.

Results

Vitamin D3 Levels

The mean baseline level of serum 25 (OH) D of all 44 participants was 23.9 ± 12.1 ng/ml (24.2 ± 13.3 ng/ml in group I and 23.5 ± 11.1 ng/ml in group II). The difference between the two groups was statistically not significant ($P > 0.05$). According to the standard levels of 25 (OH) D, 72.7% of all participants (32 of 44 patients) had low vitamin D levels in their blood. After 5 days of vitamin D3 supplementation in group I, the mean level of 25 (OH) D increased to 30.1 ± 13.2 ng/ml ($P < 0.001$).

Cardiac Troponin I Levels

Cardiac troponin I levels were elevated at baseline in each group, and were reduced after 5 days of hospitalization, $P < 0.001$. However, the mean difference of reduction between the two groups was not significant ($P > 0.05$) (Table 1).

Table 1. Cardiac troponin I levels in both study groups (Group I and Group II).

Variable	Group I (N = 22)	Group II (N = 22)	P value
	Mean ± SD	Mean ± SD	
Troponin $^{(baseline)}$ ng/ml	31.76 ± 9.68	35.04 ± 7.60	0.22
Troponin $^{(post\ treatment)}$ ng/ml	22.31 ± 7.06	23.14 ± 8.48	0.72
Mean difference ng/ml	9.45 ± 8.85	11.90 ± 9.65	0.38
P value (post-treatment vs. baseline)	<0.001	<0.001	

Data represented as Mean ± Standard deviation. Significant P value at ≤0.05.

Levels of Inflammatory Markers (hsCRP, IL-6) and WBC

Table 2 compares the levels of the inflammatory markers post-treatment vs. baseline, indicating a significant reduction in the levels of these markers in both study groups ($P < 0.05$). However, the extent of average reduction did not differ with statistical significance between the two groups, $P > 0.05$ (Table 2).

Correlation between Vitamin D at Baseline and Inflammatory Markers

A logistic regression analysis was used to estimate the correlation between the above-mentioned inflammatory markers and vitamin D levels at baseline for all 44 participants, by means of the receiver operating characteristics (ROC) curve. The test showed an inverse correlation between vitamin D levels at baseline and the levels of all inflammatory

markers; however, the correlation was only statistically significant for IL-6; it was not significant for the other markers (Figure 1).

Using the ROC curve, a low vitamin D level at baseline appears to be a good predictor for high levels of IL-6 (Figure 2).

Table 2. Levels of inflammatory markers (hsCRP, IL-6) and WBC in both study groups. Data represented as Mean ± Standard deviation

Variable	Group I (N = 22)	Group II (N = 22)	P-value
hsCRP $^{(baseline)}$ mg/l	5.66 ± 2.17	5.29 ± 2.55	0.62
hsCRP $^{(post\ treatment)}$ mg/l	3.37 ± 1.54	3.44 ± 2.21	0.91
Mean difference mg/l	2.28 ± 1.09	1.85 ± 1.48	0.28
P (post treatment vs. baseline)	<0.001	<0.001	
IL-6 $^{(baseline)}$ pg/ml	27.45 ± 9.85	25.05 ± 9.88	0.42
IL-6 $^{(post\ treatment)}$ pg/ml	21.52 ± 8.49	19.30 ± 7.97	0.38
Mean difference pg/ml	5.92 ± 8.65	5.74 ± 8.36	0.94
P (post treatment vs. baseline)	0.004	0.004	
WBC $^{(baseline)}$ x 10^9/l	11.0 ± 2.6	11.25 ± 2.7	0.79
WBC $^{(post\ treatment)}$ x 10^9/l	8.6 ± 1.8	9.7 ± 2.2	0.08
Mean difference x 10^9/l	2.4 ± 1.9	1.52 ± 1.8	0.13
P (post treatment vs. baseline)	<0.001	0.001	

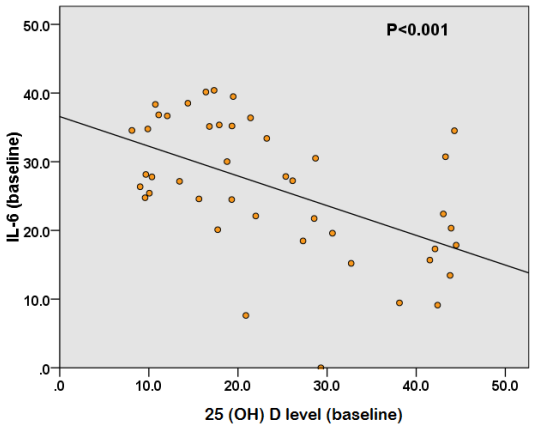

Figure 1. Significant inverse correlation between mean baseline levels of vitamin D and IL-6 in all participants (n = 44), P < 0.001.

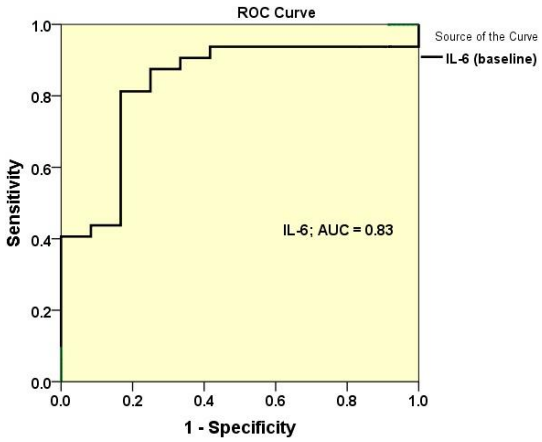

Figure 2. ROC curve of mean baseline low vitamin D levels (<30 ng/ml) as a predictor for high levels of IL-6.

Discussion

Although the incidence of CAD is decreasing in developed countries, it still represents a major health problem in most developing countries, and it is not accounted for by conventional risk factors alone [15]. Drastic changes in diet regimens and lifestyle parameters brought by global urbanization in recent decades contributed significantly to the increased incidence of CAD and diabetes [16]. This study has shown significant low plasma levels of vitamin D among STEMI patients. This finding is in agreement with other studies that also link low vitamin D levels to the rising numbers of cases of atherosclerotic heart disease, particularly AMI [17]. The results showed that after 5 days of treatment, the mean level of 25(OH)- D was significantly increased in group I [13, 18]. This increase in vitamin D, however, did not significantly affect the troponin I levels. Vitamin D supplementation may thus have either no or only minimal effect on cardiac biomarkers [19].

Although vitamin D has beneficial effects on the immune system and white blood cell counts [20], in this clinical trial there was no significant difference in post-treatment between the two study groups. This is consistent with another clinical study that showed no significant association between vitamin D supplementation and WBC changes, using 10,000 IU of vitamin D3/day therapy [21].

The salient findings of our study are:

1) the high-sensitive C-reactive protein levels at post-treatment were significantly reduced in both groups compared to baseline, without significant differences between the two groups. Trilok et al. [22] demonstrated that there was no effect of vitamin D supplement on either hsCRP or whole blood cytokine production. Their results are consistent with our finding herein regarding hsCRP. Moreover, a study by Grzanka et al. [23] demonstrated no anti-inflammatory effect of vitamin D and there was also no significant correlation between CRP and 25(OH)-D level [23]. Similar reductions were noticed with both groups in IL-6 level in the present study, indicating that vitamin D3 had no significant effects on inflammatory cytokines, particularly IL-6 [13].
2) This study also showed a significant negative correlation between the levels of vitamin D and those of IL-6 at baseline.
3) Additionally, high levels of IL-6 could predict low vitamin D levels when tested by ROC curve analysis [24]. Likewise, a previous study [25] mentioned that vitamin D3 could suppress the secretion of IL-6 level in patients with cardiovascular diseases.

It is worthwhile to mention that the study had some limitations, like the relatively small sample size due to the limitations in time and available resources. Besides, we could not manage to source a suitable placebo to have a placebo-controlled group. These measures could be easily rectified in future studies.

From our results, we conclude that although there were significant inverse correlations between baseline levels of vitamin D and interlukin-6, short-term vitamin D supplementation (5000 IU/day for 5 days) did not affect the levels of the inflammatory markers in patients with acute ST segment elevation myocardial infarction.

Acknowledgments

The authors would like to thank the technical and administrative teams in the Faculty of Medicine, University of Kufa for providing their help in finalizing this project.

Ethical Compliance

The authors have stated all possible conflicts of interest within this work. The authors have stated all sources of funding for this work. If this work involved human participants, informed consent was received from each individual. If this work involved human participants, it was conducted in accordance with the 1964 Declaration of Helsinki. If this work involved experiments with humans or animals, it was conducted in accordance with the related institutions' research ethics guidelines.

References

[1] Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. *N Engl J Med* 2012; 366 (1): 54-63.

[2] Selwyn AP, Braunwald E. Ischemic heart disease. In: Kasper LD, Fauci SA. editors. *Harrison's Principles of Internal Medicine.* 16th ed. New York: McGraw-Hill; 2004. pp. 1435-1444.

[3] Armstrong EJ, Morrow DA, Sabatine MS. Inflammatory biomarkers in acute coronary syndromes: part I: introduction and cytokines. *Circulation*. 2006; 113 (6): e72-e75.

[4] Armstrong EJ, Morrow DA, Sabatine MS. Inflammatory biomarkers in acute coronary syndromes: part II: acute-phase reactants and biomarkers of endothelial cell activation. *Circulation* 2006; 113 (7): e152-e155.

[5] Ahmed MS, Jadhav AB, Hassan A, Meng QH. Acute phase reactants as novel predictors of cardiovascular disease. *ISRN Inflammation* 2012: 953461.

[6] Fichtlscherer S, Heeschen C, Zeiher AM. Inflammatory markers and coronary artery disease. *Curr Opin Lipidol* 2004; 4 (2): 124-131.

[7] Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F; Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; 107 (3): 499-511.

[8] Ramji DP, Davies TS. Cytokines in atherosclerosis: Key players in all stages of disease and promising therapeutic targets. *Cytokine Growth Factor Rev* 2015; 26 (6): 673-685.

[9] Saxena A, Russo I, Frangogiannis NG. Inflammation as a therapeutic target in myocardial infarction: learning from past failures to meet future challenges. *Transl Res* 2016; 167 (1): 152-166.

[10] Brewer LC, Michos ED, Reis JP. Vitamin D in atherosclerosis, vascular disease, and endothelial function. *Curr Drug Targets* 2011; 12 (1): 54-60.

[11] Oh J, Weng S, Felton SK, Bhandare S, Riek A, Butler B, Proctor BM, Petty M, Chen Z, Schechtman KB, Bernal-Mizrachi L, Bernal-Mizrachi C. 1, 25 (OH) 2 vitamin D inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. *Circulation* 2009; 120 (8): 687-698.

[12] Wang L, Song Y, Manson JE, Pilz S, März W, Michaëlsson K, Lundqvist A, Jassal SK, Barrett-Connor E, Zhang C, Eaton CB, May HT, Anderson JL, Sesso HD. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: A meta-analysis of prospective studies. *Circ Cardiovasc Qual Outcomes* 2012; 5 (6): 819-829.

[13] Sokol SI, Srinivas V, Crandall JP, Kim M, Tellides G, Lebastchi AH, Yu Y, Gupta AK, Alderman MH. The effects of vitamin D repletion on endothelial function and inflammation in patients with coronary artery disease. *Vasc Med* 2012; 17 (6): 394-404.

[14] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; ESC Committee for Practice Guidelines (CPG). Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012; 60 (16): 1581-1598.

[15] Singh RB, Wilczynska A, Shastun S, Saboo B, Maheshwari A, Singh RK, De Meester F, Niaz MA, Verma NS, Bharadwai K, Chibisov S, Abramova M, Singh V. Association of chronophysiological and psychological risk factors among patients with acute coronary syndromes. *World Heart J* 2017; 9 (2): 123-134.

[16] Singh RB, Cornelissen G, Shastun S, Fedacko J. Atherosclerosis: a disease of the brain. *World Heart J* 2017; 9: 99-106.

[17] Karur S, Veerappa V, Nanjappa MC. Study of vitamin D deficiency prevalence in acute myocardial infarction. *Int J Cardiol Heart & Vessels* 2014; 3: 57-59.

[18] Arnson Y, Itzhaky D, Mosseri M, Barak V, Tzur B, Agmon-Levin N, Amital H. Vitamin D inflammatory cytokines and coronary events: a comprehensive review. *Clin Rev Allergy Immunol* 2013; 45 (2): 236-247.

[19] Muldowney S, Lucey AJ, Hill TR, Seamans KM, Taylor N, Wallace JM, Horigan G, Barnes MS, Bonham MP, Duffy EM, Strain JJ, Cashman KD, Kiely M. Incremental cholecalciferol supplementation up to 15 μg/d throughout winter at 51–55 N has no effect on biomarkers of cardiovascular risk in healthy young and older adults. *J Nutr* 2012; 142 (8): 1519-1525.

[20] Lange NE, Litonjua A, Hawrylowicz CM, Weiss S. Vitamin D, the immune system and asthma. *Expert Rev Clin Immunol* 2009; 5 (6): 693-702.

[21] Soliman AT, Eldabbagh M, Elawwa A, Saleem W. Does Vitamin D therapy affect hematological indices in

adolescents with vitamin D deficiency? *Indian J Endocrinol Metab* 2012; 16 (4): 659–660.

[22] Trilok-Kumar G, Arora H, Rajput M, Chellani H, Singh V, Raynes J, Arya S, Aggarwal S, Srivastava N, Sachdev HP, Filteau S. Effect of vitamin D supplementation of low birth weight term Indian infants from birth on cytokine production at 6 months. *Eur J Clin Nutr* 2012; 66 (6): 746-750.

[23] Grzanka A, Machura E, Mazur B, Misiolek M, Jochem J, Kasperski J, Kasperska-Zajac A. Relationship between vitamin D status and the inflammatory state in patients with chronic spontaneous urticaria. *J Inflamm* 2014; 11 (1): 2-6.

[24] Jablonski KL, Chonchol M, Pierce GL, Walker AE, Seals DR. 25-hydroxyvitamin D deficiency is associated with inflammation-linked vascular endothelial dysfunction in middle-aged and older adults. Hypertension 2011; 57 (1): 63-69.

[25] Ku YC, Liu ME, Ku CS, Liu TY, Lin SL. Relationship between vitamin D deficiency and cardiovascular disease. *World J Cardiol* 2013; 5 (9): 337- 346.