



## Assessment of long term prognostic value of admission vitamin D level in patients with acute STEMI undergoing primary percutaneous coronary intervention

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### Abstract

**Objective:** Vitamin-D status is very important for optimal function of human body especially cardiovascular system. The aim of this study was to investigate the long term prognostic value of admission vitamin D level in acute ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI).

**Methods:** One hundred fifty seven consecutive patients, who were admitted to a training and research hospital with a diagnosis of STEMI and underwent PPCI, were recruited in this prospective study. The study patients were divided into 2 groups according to their vitamin-D levels as follows: High vitamin-D group (n=80) and Low vitamin-D group (n=77). The severity of coronary artery disease (CAD) was assessed with calculation of the SYNTAX score.

**Results:** There were significant negative correlations between Vitamin-D level and SYNTAX score, serum glucose, and gender, but a positive correlation with hemoglobin level. Cardiovascular mortality was found to be significantly higher in the low vitamin-D group as compared to the high group (p<0.001). In multivariate analysis, low vitamin-D level was found as a significant independent predictor of long term cardiovascular mortality after adjusting for other risk factors.

**Conclusion:** We demonstrated that low admission vitamin-D is related to severity of CAD. Vitamin-D deficiency is an independent predictor for long term cardiovascular mortality in acute STEMI undergoing PPCI.

**Keywords:** Vitamin D; Mortality; SYNTAX score.

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## Primer perkutan girişim uygulanan akut STEMI hastalarda başvuru D vitamini düzeyinin uzun dönem prognostik değeri

### Öz

**Amaç:** Vitamin-D, insan vücudunda özellikle kardiyovasküler sistemin işlevi için çok önemlidir. Bu çalışmanın amacı, primer perkütan koroner girişim (PPCI) uygulanan akut ST-segment yükselmeli miyokard infarktüsünde (STEMI), hastane başvurusu sırasındaki D vitamini düzeyinin uzun dönem prognostik değerini araştırmaktır.

**Yöntemler:** Bu prospektif çalışmada, eğitim ve araştırma hastanesine STEMI tanısı ile başvuran ve PPCI uygulanan ardışık 157 hasta alındı. Çalışma hastaları başvuru vitamin-D düzeylerine göre 2 gruba ayrıldı: Yüksek vitamin-D grubu (n = 80) ve düşük vitamin-D grubu (n = 77). Koroner arter hastalığının şiddeti SYNTAX skoru ile hesaplandı.

**Bulgular:** Vitamin-D düzeyi ile SYNTAX skoru, serum glikozu ve cinsiyet arasında anlamlı negatif korelasyon vardı, fakat hemoglobin düzeyi ile pozitif korelasyon vardı. Kardiyovasküler mortalite, düşük vitamin-D grubunda, yüksek gruba göre anlamlı olarak daha yüksek bulundu (p <0.001). Çok değişkenli analizde, düşük vitamin-D düzeyinin, diğer risk faktörlerini ayarladıktan sonra uzun vadede kardiyovasküler mortalitenin anlamlı bağımsız bir göstergesi olduğu bulunmuştur.

**Sonuç:** Düşük başvuru vitamin D düzeyinin koroner arter hastalığı şiddeti ile ilişkili olduğunu gösterdik. Vitamin-D eksikliği, PPCI uygulanan akut STEMI'de uzun süreli kardiyovasküler mortalite için bağımsız bir belirleyicidir.

**Anahtar kelimeler:** D vitamini; Ölüm; SYNTAX puanı.

### INTRODUCTION

Vitamin-D status is very important for optimal function of human body especially cardiovascular system<sup>1</sup>. It inhibits renin-angiotensin system and affects endothelial and platelet functions, insulin resistance, blood pressure and inflammatory process<sup>2-4</sup>. Vitamin-D deficiency has been reported to be common in acute myocardial infarction<sup>5</sup>. Moreover, emerging data indicate a significant relationship between vitamin-D deficiency and coronary artery risk factors and other cardiovascular disease. It leads to development of hypertension, diabetes, chronic renal failure, metabolic syndrome, left ventricular hypertrophy, chronic vascular inflammation and heart failure<sup>6,7</sup>. An important association between vitamin D deficiency and raised risk of major adverse cardiovascular events were reported in a previous study<sup>8</sup>. Low levels of vitamin D were demonstrated to be related with post-myocardial infarction left ventricular dysfunction due to remodelling, which results in sudden cardiac death and heart failure mortality<sup>9,10</sup>.

Although there are few studies which were evaluated the associations between vitamin-D levels and in-hospital and short and middle term major adverse cardiovascular events including mortality in acute coronary syndrome<sup>11-13</sup>, precise link between them still unknown due to lack of data in terms of long term survival data. Hence, we aimed to investigate the long term prognostic value of admission vitamin D level in patients with acute ST segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI). We hypothesized that reliable data showing the possible effect of vitamin-D deficiency on long term cardiovascular mortality will be reported with this study.

### METHODS

One hundred fifty seven consecutive patients, who were admitted to a training and research hospital with a diagnosis of STEMI and underwent primary PCI between June 2012 and December 2012, were recruited in this prospective study. The inclusion criteria were as follows: (1) presentation within 12 h of the

onset of symptoms (typical chest pain lasting for >30 min), (2) ST-segment elevation of at least 2 mm in at least two contiguous electrocardiographic (ECG) leads or new onset of complete left bundle branch block, (3) increased serial serum markers of myocardial damage >2-fold over the upper normal range for creatine kinase (CK) and troponin I, (4) treatment by primary PCI (angioplasty and/or stent deployment).

Exclusion criteria of the present study were as follows: age >90 years, no indication for primary PCI, coronary anatomy unfavorable for PCI, loss to follow-up of patients, myopericarditis, acute or chronic infection, malignancy, severe kidney or liver disorders, acute or chronic heart failure, acute or chronic inflammatory disease, history of autoimmune disease, use of drugs affecting vitamin-D or calcium levels or parathyroid gland functions such as steroids, calcium supplements, thiazide diuretics.

The study patients were divided into 2 groups according to their admission vitamin-D levels as follows: High vitamin-D group (n=80) and Low vitamin-D group (n=77). All primary PCI procedures were performed in a single, large-volume tertiary care centre (> 3000 PCI/year) by expert operators who perform an average of > 75 PCIs per year.

Demographical, clinical, laboratory, echocardiographic and coronary angiography data were obtained. A 12-lead ECG was recorded in each patient just after hospital admission, and the type of myocardial infarction (MI) was also determined based on the ECG criteria. All study participants were taken standart guideline based therapy and coronary revascularization procedure at the discretion of the attending physician. Moreover, all patients underwent transthoracic echocardiography examinations (Vivid 3; General Electric, Milwaukee, Wis.) to evaluate the left ventricular ejection fraction (LVEF). The severity of CAD was assessed with

calculation of the SYNTAX score by two expert interventional cardiologists who were independent from patient's data. Eligible patients were between 18 and 90 years of age and all were able to provide written informed consent, which was a prerequisite for enrollment. The study complies with the Declaration of Helsinki, and the trial protocol was approved by the local Ethics Committee (number:47; date: 06/10/2011).

All patients received a chewable 300 mg aspirin and clopidogrel (600 mg loading dosage) before coronary angiography procedure. Angiographic data of the patients were evaluated from catheter laboratory records. Emergency coronary angiography and angioplasty were performed by percutaneous femoral approach. A non-ionic, low-osmolality contrast medium was used in all patients. The artery that was presumed to be unobstructed was injected first. Blood flow in the infarct-related artery (IRA) was graded according to the Thrombolysis in Myocardial Infarction (TIMI) classification. Heparin (100 IU/kg) was administered when the coronary anatomy was first defined. An angiographic evaluation was made by visual assessment. Primary angioplasty, including balloon angioplasty and/or stent implantation, was performed only for IRA according to the lesion type. For each procedure, interventional success at the acute phase was defined as reducing obstruction and stenosis to 30% of the IRA with TIMI 3 flow just after primary angioplasty. After angioplasty, all patients were admitted to the coronary care unit, where 100 mg of aspirin and 75 mg of clopidogrel were given.

On admission, venous blood was obtained from all patients included in the study before coronary angiography in ethylene diamine tetra-acetic acid (EDTA) added tubes and serum separator tubes. All plain tubes were centrifuged at 1400 rpm for 10 minutes within 30 min of collection. The sera was then separated, stored in aliquots, and kept frozen at

-80 °C until vitamin D analysis. Serum Vitamin D levels were analyzed by chemiluminescent method with Cobas- e 411 biochemical analyzer (Roche Diagnostics, USA). Platelet, lymphocyte, neutrophil and white blood cell counts were measured as part of the automated complete blood cell count using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc., Mervue, Galway, Ireland). Within 24 h of admission, creatine kinase-myocardial band (CK-MB) and high sensitive troponin T levels were measured by Cobas e 411 analyzer (Roche Diagnostics, USA) with chemiluminescence method in whole blood samples. Twelve hour fasting serum levels of triglycerides and total, low-density lipoprotein (LDL), and high density lipoprotein (HDL) cholesterol were measured by standard enzymatic methods. Other biochemical measurements were carried out by using standard methods.

Diabetes was defined as a previous history of the disease, use of dietary treatment, insulin or oral antidiabetic drugs, or fasting venous blood glucose level  $\geq 126$  mg/dl on two occasions in previously untreated patients. Hypertension was diagnosed as systolic blood pressure  $>140$  mmHg and/or diastolic blood pressure  $>90$  mmHg, or use of antihypertensive drugs. Smoking was defined as the active regular use of cigarettes.

Follow-up data of the study participants were obtained from hospital records or by interviewing patients, their families, or their family physicians (directly or by telephone). The primary end-point of the study was cardiovascular mortality, which was defined as unexplained sudden death or death due to acute STEMI, acute decompensated heart failure or hemodynamically significant arrhythmia.

Statistical Analysis: All statistical analyses were carried out using SPSS statistical software, version 19.0 (SPSS Inc., Chicago, IL, USA). The variables were investigated by using visual

(histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Non-parametric values were expressed as median (minimum-maximum). Continuous variables were expressed as mean $\pm$ standard deviation, and categorical variables were expressed as a percentage. A comparison of the parametric values between the two groups was performed by a two-tailed Student's t test. Categorical variables were also compared by the likelihood ratio chi<sup>2</sup> or Fisher's exact test. The Spearman correlation coefficient was calculated for the comparison of two data sets. A backward stepwise multivariate Cox regression analysis, which included variables with  $p < 0.1$ , was performed to identify independent predictors of long-term cardiovascular mortality. Cumulative survival curves for long term cardiovascular mortality were constructed using the Kaplan-Meier method and compared using the log-rank test. Statistical significance was indicated by a two sided p value less than 0.05.

## RESULTS

One hundred fifty seven patients were included in this study. Baseline demographic, clinical and laboratory characteristics of the study groups were summarized in Table 1. Male gender was significantly higher in the high vitamin-D group than in the low group. Moreover, total cholesterol, low-density lipoprotein cholesterol, admission blood hemoglobin were found to be higher in the high vitamin-D group than in the low vitamin-D group. However, red cell distribution width and admission blood glucose were lower in the high group compared to low group. As expected, vitamin-D levels were significantly higher in the high group than in the low group. SYNTHAX score, which is an important score related to severity of coronary artery disease, was significantly higher in the low vitamin-D group than the high group.

Table 1. Baseline characteristics of study patients (n:157)

	Low D vitamin group (n:77) [n (%), median (min-max) or mean±SD]	High D vitamin group (n:80) [n (%), median (min-max) or mean±SD]	p value
Age, years	55,5±13,2	54,0±12,1	0,48
LVEF(%)	49,1± 8,9	47,9 ± 9,2	0,46
Male gender (n)	56 (72.7)	71 (88.8)	0,011
Diabetes mellitus (n)	39 (50.6)	35 (43.5)	0.39
Hypertension (n)	38 (49.4)	37 (46.3)	0,7
Current smoker (n)	34(44.2)	38 (47.5)	0.67
Vitamin D level	5,8(3-8,7)	12,8(8,7-62)	<b>&lt;0,001</b>
SYNTAX score	15,5±3,3	12±3,5	<b>&lt;0,001</b>
Uric acid	5,2±0,18	5,4±0,14	0,53
Platelet counts (×10 <sup>9</sup> /L)	263 (117-447)	249(132-444)	0,21
WBC (×10 <sup>9</sup> /L)	11,2± 2,7	12,1 ± 3,0	0,10
Creatinine (mg/dL)	0,9 (0,5-10,7)	0,9 (0,5-2,3)	0,30
C-Reactive Protein (mg/L)	19,9 (0,7-332)	17 (1,0-280)	0,45
RDW (%)	13,2±1,3	12,8±1,0	0,03
Troponin I (ng/ml)	3,5 (0,01-50)	5,0 (0,01-50)	0,55
Total Cholesterol (mg/dl)	181,6 ± 40,6	194,8 ±35,5	<b>0,03</b>
LDL-Cholesterol (mg/dl)	122,8 ±37,1	136,2 ±33,3	<b>0,02</b>
HDL-Cholesterol (mg/dl)	40,3± 11,7	38,7 ± 7,6	0,32
Triglyceride (mg/dl)	101 (28-321)	120 (43-547)	0,13
Glucose (mg/dl)	137 (84-361)	122 (79-371)	<b>0,014</b>
Hemoglobin, (g/dl)	13,5 ±1,9	14,4 ± 1,5	<b>0,002</b>
Hemoglobin A1c (%)	6,4±1,5	6,2 ±1,4	0,34
MPV (pL)	8,74 ± 0,91	8,71± 0,97	0,85
Cardiovascular mortality (n)	10 (13)	1(1,3)	<b>0,004</b>
infarct related artery (n)			0,75
Left anterior descending	32	38	
Circumflex	12	11	
Right	24	26	
Bypass graft	1	1	
Follow-up (months)	31,9±8,4	34,8±2,8	<b>0,004</b>

SD=standart deviation, LDL= low-density lipoprotein, HDL= High-density lipoprotein, CK-MB= Creatinine kinase-MB, WBC= white blood cell, MPV= mean platelet volume, RDW= red blood cell distribution width.

There was significant negative correlations between Vitamin-D level and SYNTAX score (r=-0.451, p<0.001), serum glucose (r=-0.191, p=0.017), and gender (r=-0.186, p=0.02), but a positive correlation with hemoglobin level (r=0.231, p =0.004) (Table 2). During the course of the present study (median follow-up period of 31.9±8.4 vs. 34.8±2.8 months for low

and high vitamin-D groups respectively), 11 deaths occurred out of 157 patients (7%). Cardiovascular mortality was found to be significantly higher in the decreased vitamin-D group (n:10) as compared to the increased vitamin-D group (n:1) (12.9% vs 1.2%, respectively; p<0.001).

Table 2: Spearman’s correlations analysis between vitamin D and other parameters

Variable	r value	p value
SYNTAX score	-0.451	<0.001
Admission blood glucose (mg/dl)	-0.191	0.017
Admission blood hemoglobin (g/dl)	0.231	0.004
Gender	-0.186	0.02

The Kaplan–Meier survival plot for cardiovascular mortality in both groups is presented in Figure 1. The independent predictors for cardiovascular mortality including age, creatinine, hemoglobin, vitamin-D level and left ventricular ejection fraction were included in a Cox regression model and analyzed in a stepwise fashion. In the multivariate analysis, low vitamin-D level (odds

ratio [95% confidence interval]: 12.37 [1.169–131.01], p = 0.037) and age (1.102 [1.003–1.212], p = 0.044) were found as significant independent predictors of long term cardiovascular mortality after adjusting for other risk factors that had been found as significant predictors in the univariate analysis (Table 3).

Table 3. The independent predictors of mortality.

	Univariate			multivariate		
	OR	CI	P	OR	CI	P
Low vitamin D group	11.8	1,47-94,5	0,02	12,37	1,169-131,01	<b>0,037</b>
Age	1,120	1,049-1,196	0,001	1,102	1,003-1,212	<b>0,044</b>
Creatinine (mg/dL)	4,56	0,964-21,62	0,056			
Hemoglobin (g/dl)	0,63	0,46-0,857	0,003			
LVEF(%)	0,93	0,86-1,00	0,057			

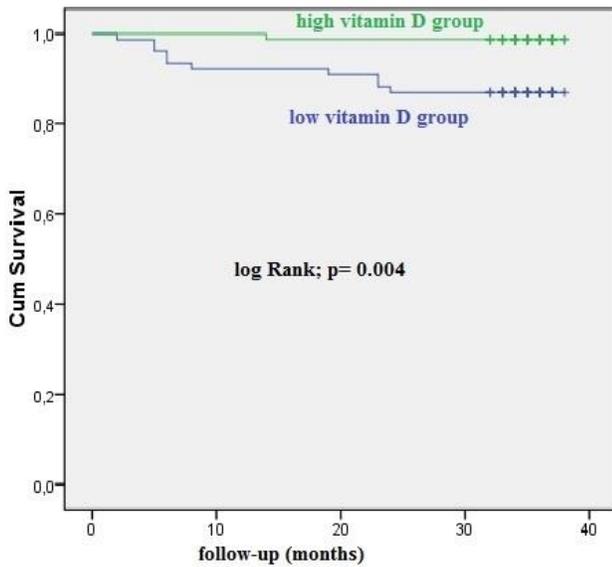
OR= odds ratio, CI= confidence interval.

### DISCUSSION

Vitamin-D deficiency was significantly related with severity of coronary artery disease defined as SYNTAX score. Moreover, it was found to be a strong independent predictor of long term cardiovascular mortality in patients with acute STEMI undergoing primary percutaneous coronary intervention.

Vitamin-D receptors are found in immune cells, endothelial cells, cardiomyocytes, pancreatic beta-cells, neurons and osteoblasts<sup>1,14</sup>. Sources of vitamin D hormones include exposure to ultraviolet light, certain foods, and dietary

supplements<sup>15</sup>. Vitamin-D deficiency has been reported in acute myocardial infarction, heart failure, stroke, restenosis, diabetes and peripheral arterial disease<sup>1</sup>. Major risk factors for vitamin-D deficiency are aging, increased distance from the equator, winter seasons, darkly pigmented skin, smoking, obesity, physical inactivity, genetic factors, malabsorption, renal and liver diseases and some drugs<sup>1</sup>. Large epidemiological and observational studies reported an association between vitamin-D deficiency and cardiovascular events in healthy subjects<sup>16,17</sup>.



**Figure 1.** Kaplan-Meier curves for long term survival according to vitamin D group. The long term cardiovascular mortality was 1.3% in the high vitamin D group versus 13% in the low vitamin D group (log rank,  $P=0.004$ ).

Metrio et al. reported a significant independent association between low vitamin-D level and worse prognosis in terms of in-hospital and 1-year major adverse cardiovascular events in acute coronary syndromes<sup>11</sup>. Moreover, Correia et al. demonstrated a relationship of low vitamin-D level with in-hospital cardiovascular mortality<sup>12</sup>. Other large clinical study by the Ng et al. reported an important association between lowest vitamin-D quartile and long term major cardiovascular events notably rehospitalization for heart failure<sup>18</sup>. NHANES III study was also demonstrated a U-shaped association between 25 (OH) D and slight increased mortality at high levels. Moreover, it reported an inverse link between vitamin-D and mortality<sup>19</sup>. Similar relation between vitamin-D deficiency and in-hospital mortality was found by the study of Khalili et al<sup>20</sup>. Our study, concordant with previous studies in the literature, strengthen the evidence of a significant relationship between vitamin-D deficiency and poor cardiovascular outcomes. Furthermore, a direct association was found

between vitamin-D status and severity of coronary lesions indicated by the SYNTAX score. However, our study had small size population and had few mortality rate especially in high vitamin-D group.

The possible pathophysiological link between vitamin-D deficiency and cardiovascular events is unknown. Vitamin-D deficiency lead to hyperparatiroidism, trigger of the renin angiotensin- aldosterone system, hypertrophy and remodeling of both the vascular smooth muscle and left ventricle myocardium, increased insulin resistance due to pancreatic beta cell dysfunction, severe inflammation and cytokine release results in atherosclerosis and it's cardiovascular complications<sup>21-22</sup>. Endothelial dysfunction, which is one of the adverse effect of vitamin-D deficiency, may stimulate platelet activation and aggregation results in acute coronary thrombosis, severe vasoconstriction and neoangiogenesis, which play a crucial role in developing of acute STEMI<sup>23</sup>.

### Study Limitations

The present study has some limitations. First, it arose from single center so that only patients admitted to our center could be enrolled. Second, study population was very small and mortality rates were underpowered to present a reliable and more accurate relation between vitamin-D deficiency and long term cardiovascular mortality. Third, many factors that affect vitamin D-level such as latitude, sunlight exposure, skin color, serum calcium and albumin, dietary vitamin intake, season, parathyroid gland status were not taken into consideration in this study. Hence, they may affect our study results. Fourth, since this study design was not randomized controlled, we could not say any causal association between vitamin-D deficiency and long term long term cardiovascular mortality in this setting.

## CONCLUSION

We demonstrated that low admission vitamin-D is related to severity of coronary artery disease. Vitamin-D deficiency is an independent predictor for long term cardiovascular mortality in patients with acute STEMI undergoing primary percutaneous coronary intervention. Vitamin-D supplementation in the state of deficiency may be a promising strategy for primary prevention of acute myocardial infarction. Randomized controlled clinical trials with large population cohorts are needed to elucidate this relation.

32. Uluslararası Katılımlı Türk Kardiyoloji Kongresinde (2016,ANTALYA) poster bildirisi olarak sunuldu. [PS2-18].Assessment of long term prognostic value of admission vitamin D level in patients with acute ST segment elevation myocardial infarction undergoing primary percutaneous coronary intervention.

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