Original Article

The Prevalence and Prognostic Role of Vitamin D Deficiency in Patients with Acute Coronary Syndrome: A Single Centre Study in South-West of Iran

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Background: **The objectives of this study were estimating the prevalence of vitamin D deficiency in patients with acute coronary syndrome comparing with normal people and evaluating the relationship between vitamin D deficiency and short-term mortality in these patients.**

Methods: **We considered 106 patients with non-ST elevation myocardial infarction and high-risk unstable angina and 110 patients with ST elevation myocardial infarction as group A. The control group (group B) consisted of 120 individuals without any known cardiovascular diseases or systemic disease. We measured serum 25-hydroxyvitamin D in all cases and classified them according to their serum 25-hydroxyvitamin D levels. Sufficient vitamin D level was considered $\geq$30 ng/ml. We followed the patients for 30 days after index admission.**

Results: **The prevalence of hypovitaminosis D in group A was much higher than group B. In group A, 72% of patients had serum 25-hydroxyvitamin D level of 20 ng/ml or less. This percentage was only 27.4% in control group. We did not find any significant relationship between vitamin D deficiency and short-term mortality in patients with acute coronary syndrome.**

Conclusion: **Our data suggest that vitamin D deficiency was present in most of patients admitted with acute coronary syndrome in Ahvaz.**

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Keywords. Vitamin D; Acute coronary syndrome; Prevalence; Prognosis

Introduction

Some studies suggest vitamin D deficiency may be linked to cardiovascular disease. The association between coronary artery disease and vitamin D has been reported in many observational studies. According to these studies, inadequate vitamin D intake and vitamin D deficiency are associated with coronary artery disease risk factors such as dyslipidaemia, hypertension, diabetes mellitus, obesity and even factors such as small dense low-density lipoprotein cholesterol concentration, lipoprotein-associated phospholipase A_2 activity and high-sensitivity C-reactive protein levels [1–4]. In the Health Professional Follow-up Study, 10-year follow-up of 18,225 men showed low levels of vitamin D were associated with higher risk of myocardial infarction, even after controlling for other risk factors [5]. On the other hand at least a case–control study in India found that vitamin D had a deleterious effect on ischaemic heart disease [2].

Vitamin D deficiency is common around the world. Zadshir et al. reported that the prevalence of hypovitaminosis D in United States had been 40% in adult men and 50% in adult women [6]. According to previous studies, vitamin D deficiency is common in most parts of Iran [7,8]. We did not have any data about its prevalence among our patients. Therefore, we designed an observational cohort study aimed at determining the prevalence of vitamin D deficiency in patients admitted with acute coronary syndrome and evaluating the relation between vitamin D deficiency and short-term mortality in these patients.

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Methods

The patients included in the study were selected consecutively among those admitted with acute coronary syndrome from September 2011 to March 2012 at affiliated hospitals of Jundishapur University of Medical Sciences. We considered patients with non-ST elevation myocardial infarction (NSTEMI) and high-risk unstable angina and patients with ST elevation myocardial infarction (STEMI) who had been living in Ahvaz during two last years as group A.

The criteria for selecting cases as unstable angina were age more than 30 and presence of high risk unstable angina characteristics including (1) accelerating tempo of chest pain during preceding 48 h or resting chest pain lasting more than 20 min (2) new ST depression or T inversion in electrocardiogram (ECG) leads or new regional wall motion abnormality in transthoracic echocardiography (3) hypotension, pulmonary oedema or worsening of crackles, new S_3 and new mitral regurgitation murmur resulting from ischaemia.

The inclusion criteria for selecting patients as STEMI was presence of acute ST elevation myocardial infarction in patients older than 30 on the basis of these characteristics: (1) resting chest pain lasting more than 30 min (2) typical ischaemic ST elevation in electrocardiogram (ECG) leads (3) rising of serum cardiac enzymes concentration (CK-MB and Troponins).

The control group (group B) consisted of individuals without any known cardiovascular diseases, hypertension and any systemic disease requiring long-term drug therapy.

We recruited the cases of group B among the medical staff and their family members at the same period of time. We considered healthy persons who had been living in Ahvaz during last two years and were older than 30 and their cardiovascular physical examination including blood pressure was normal. We excluded individuals who had any known cardiovascular disease or chronic diseases like known renal or hepatic disease, endocrine and metabolic diseases like known diabetes mellitus (DM), hyperthyroidism or hyperparathyroidism, mal-absorption, bone disease, known malignancy, pregnancy or lactation, immobility for more than one week, recent vitamin D injection (oral during recent two weeks or injection during last six months) or receiving drugs affecting vitamin D and calcium metabolism like corticosteroid or anti-epilepsy drugs. Out of 120 control cases, 105 persons were selected from 45 families.

All cases underwent a standard 12-lead ECG and echocardiographic examination. Patients were imaged in the left lateral decubitus position in the parasternal and apical views during the first day of admission. Left ventricular ejection fraction was calculated from the conventional apical two- and four-chamber images, using the biplane Simpson's technique. Blood samples were obtained immediately after admission. We measured biochemical parameters including 25-hydroxyvitamin that was measured by an electrochemiluminescence technology using Cobas e601 module (Roche Diagnostics, Mannheim, Germany). The patients' sera were kept at 2–8 °C and transferred to the laboratory on Saturdays, Mondays and Wednesdays.

Serum triglyceride, total cholesterol, LDL, HDL, fasting blood sugar, creatinine, BUN, haemoglobin concentrations were expressed as milligrams per decilitre (mg/dl) and serum sodium and potassium were expressed as milliequivalent per litre (meq/L) Serum creatine kinase-MB were measured quantitatively and troponin T was detected qualitatively.

Body weight and height were measured during admission and Body Mass Index (BMI) was calculated.

Hypertension was defined as taking antihypertensive drugs or baseline blood pressure equals to 140/90 mmHg or more. Diabetes mellitus (DM) was defined as taking hypoglycaemic agents or fasting plasma glucose level at or above 126 mg/dl, a 2-h value in an oral glucose tolerance test at or above 200 mg/dl, or a random plasma glucose concentration $\geq$200 mg/dl in the presence of symptoms. Hyperlipidaemia was defined as a total cholesterol level $\geq$220 mg/dl or a triglyceride level $\geq$150 mg/dl. Active smoking was defined current use of cigarette, hookah or pipe.

Normal level of serum 25-hydroxyvitamin D was defined $\geq$30 ng/ml. Hence, serum levels less than 30 ng/ml were considered hypovitaminosis D.

We classified the patients according to their 25-hydroxyvitamin D levels into three groups. Patients with sufficient vitamin D level had 25-hydroxyvitamin D level $\geq$30 ng/ml. Patients with insufficient vitamin D level had 25-hydroxyvitamin D level between 30 and 20 ng/ml and vitamin D deficient patients had 25-hydroxyvitamin D level $\leq$20 ng/ml.

ASA, beta blockers, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers and statins were prescribed for all of the patients during admission and after discharge. The patients underwent selective coronary angiography and revascularisation according to current guidelines. We followed the patients for 30 days after admission.

The primary aims of the study were determination of vitamin D deficiency prevalence among patients admitted with acute coronary syndrome comparing with control group and evaluating the relationship between in-hospital and 30-day cardiovascular mortality and vitamin D deficiency.

The study protocol was approved by ethics committee of Jundishapur University of Medical Sciences. All patients provided written informed consent.

Continuous data were expressed as mean $\pm$ standard deviation values.

Fisher's exact test, Chi-square test and student *T*-test were used to compare groups. A *P* value less than 0.05 was considered to be statistically significant.

Results

The study population consisted of 216 patients as acute coronary syndrome group (Group A that consisted of 110 patients with STEMI and 106 patients with high risk

Table 1. *Baseline Characteristics of Cases in Group A (Acute Coronary Syndrome) and Group B (Control).*

Variable	Group A ($N = 216$)	Group B ($N = 120$)	P value
Age (years)	61.44 ± 10.96 (39–83)	54.95 ± 12.3 (35–82)	0.11
Male/female	125 (58%)/91 (42%)	58 (48.3%)/62 (51.7%)	0.09
Weight (kg)	72.68 ± 12.04 (45–110)	71.49 ± 13.28 (54–112)	0.85
BMI (kg/m^2)	25.67 ± 3.99 (17–42)	24.45 ± 3.35 (17.2–39)	0.36
Hypertension, *n*	142 (65.7%)	0	0.00*
Previous cerebrovascular accident, *n*	7 (3.3%)	0	0.01*
Peripheral arterial disease, *n*	5 (2.3%)	0	0.01*
Prior coronary artery bypass surgery, *n*	6 (3%)	0	0.01*
Prior percutaneous coronary intervention, *n*	4 (2%)	0	0.01*
Systolic blood pressure (mmHg)	131.69 ± 24.39 (80–200)	119.13 ± 8.37 (100–135)	0.00*
Diastolic blood pressure (mmHg)	78.85 ± 13.97 (40–120)	73.53 ± 5.19 (55–100)	0.00*
Heart rate (*n*/min)	77.88 ± 15.26 (49–140)	78.22 ± 12.03 (55–100)	0.83
Smoking, *n*	70 (32.4%)	12 (%10)	0.02*
Dyslipidaemia, *n*	98 (45.4%)	20 (%17)	0.03*
Diabetes mellitus, *n*	141 (65.2%)	0	0.00*
Fasting blood sugar (mg/dl)	174.88 ± 100.62 (63–489)	93.98 ± 6.09 (75–110)	0.00*
Creatinine (mg/dl)	1.33 ± 0.61 (0.5–4.2)	1.16 ± 0.11 (0.5–1.6)	0.19
BUN (mg/dl)	22.38 ± 13.27 (7.9–98)	15.31 ± 2.98 (7.2–35)	0.02*
Haemoglobin	13.69 ± 1.86 (7.8–15)	13.73 ± 1.12 (11.2–16.1)	0.30
Triglyceride (mg/dl)	154.47 ± 91.44 (45–310)	146.91 ± 47.21 (55–210)	0.09
Total cholesterol (mg/dl)	197.42 ± 47.04 (94–366)	190.16 ± 39.62 (100–230)	0.13
LDL (mg/dl)	122.57 ± 38.77 (60–306)	118.87 ± 35.54 (60–210)	0.17
HDL (mg/dl)	38.77 ± 6.84 (24–55)	40.66 ± 8.94 (27–88)	0.11
Sodium (meq/L)	139.18 ± 4.08 (130–149)	140.03 ± 2.02 (134–148)	0.71
Potassium (meq/L)	4.22 ± 0.44 (3.1–6.3)	4.32 ± 0.24 (3.7–5.3)	0.51
25-Hydroxyvitamin D (ng/ml)	18.66 ± 19.97 (3.7–233)	43.56 ± 38.19 (4–245)	0.00*

* Statistically significant difference between two groups ($P < 0.05$).

unstable angina or NSTEMI) and 120 persons as control group (Group B).

The baseline characteristics of cases in group A and group B are presented in Table 1.

Except hypertension and DM that did not exist in control group, there were significant differences in BUN levels and smoking and dyslipidaemia prevalence between two groups. The other significant difference was in mean serum 25-hydroxyvitamin D levels. ASA, ACE inhibitor or angiotensin II antagonist, beta blocker, statin, diuretic and calcium channel blocker had been received by 102 (47%), 67 (31%), 76 (35%), 81 (38%), 7 (3%) and 6 (2.7%) of patients, respectively. None of our patients had received vitamin D or calcium supplements during last three months.

We categorised the cases in each group into four subgroups according to their serum 25-hydroxyvitamin D levels that is presented in Fig. 1. The prevalence of hypovitaminosis D in group A was much higher than control group and the difference was statistically significant.

We also categorised the patients in group A to two groups according to their serum 25-hydroxyvitamin D levels. The baseline characteristics of cases in this group

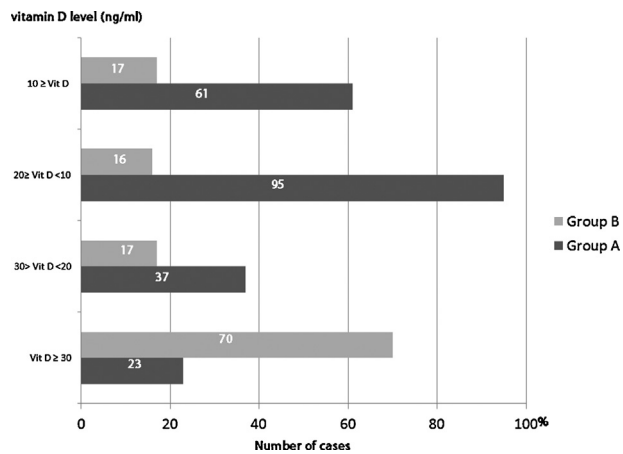

Figure 1. *Comparing the number of cases with different serum 25-hydroxyvitamin D levels in acute coronary syndrome patients (group A) versus control cases (group B).*

Table 2. *Baseline Characteristics of Patients in Group A with Low 25-Hydroxyvitamin D Levels Compared with Patients with Normal 25-Hydroxyvitamin D Levels.*

Variable	30> ($N = 192$)	≥30 ($N = 24$)	P value
Age (years)	65.70 ± 10.05	60.89 ± 10.99	0.06
Male/female	77/115	11/12	0.10
Weight (kg)	73.13 ± 12.49	69.48 ± 6.70	0.17
BMI (kg/m^2)	25.71 ± 4.14	25.36 ± 4.77	0.39
Hypertension, *n*	127	14	0.64
Systolic blood pressure (mmHg)	133.26 ± 24.79	120.00 ± 16.31	0.01*
Diastolic blood pressure (mmHg)	78.16 ± 15.24	75.43 ± 10.76	0.20
Heart rate (*n*/min)	78.16 ± 15.50	75.48 ± 13.47	0.42
Smoking, *n*	67	3	0.10
Dyslipidaemia, *n*	86	12	0.51
Diabetes mellitus, *n*	128	12	0.17
Fasting blood glucose (mg/dl)	177.29 ± 104.18	150.91 ± 60.91	0.06
Creatinine (mg/dl)	1.33 ± 0.61	1.27 ± 0.68	0.71
BUN (mg/dl)	22.52 ± 13.66	20.74 ± 9.63	0.37
Haemoglobin	12.56 ± 1.79	12.48 ± 1.62	0.85
Triglyceride (mg/dl)	155.93 ± 95.01	140.26 ± 48.80	0.61
Total cholesterol (mg/dl)	198.35 ± 48.22	190.39 ± 33.78	0.23
LDL (mg/dl)	123.01 ± 36.64	118.87 ± 32.03	0.67
HDL (mg/dl)	38.41 ± 4.96	41.57 ± 15.35	0.09
Sodium (meq/L)	139.18 ± 4.21	139.17 ± 3.11 (130–150)	0.51
Potassium (meq/L)	4.23 ± 0.48	4.22 ± 0.51	0.50

* Statistically significant difference between two groups ($P < 0.05$).

compared with control group are presented in Table 2. The patients with normal serum 25-hydroxyvitamin D levels were younger and had lower fasting blood glucose levels, although those were not significantly different. The only significant difference between two groups of patients was systolic blood pressure that was lower in patients with normal 25-hydroxyvitamin D levels.

Among our patients, 82 (37.9%) cases had BMI ≤25 and the mean of serum 25-hydroxyvitamin D was 20.7 ± 1.9 ng/ml in this group. Twenty-six (12.1%) patients had BMI of ≥30 and their mean serum 25-hydroxyvitamin D was 17.0 ± 3.3 ng/ml. The mean of serum 25-hydroxyvitamin D was 13.6 ± 1.3 ng/ml in the rest of patients (50%). Thus the serum 25-hydroxyvitamin D levels in patients with higher BMI were lower than patients with lower BMI but this difference was not significant (P value: 0.16).

Seventy-one (32.8%) patients were smokers and the mean of serum 25-hydroxyvitamin D levels was 14.6 ± 7.8 ng/ml in this group. The mean of serum 25-hydroxyvitamin D levels was 23.50 ± 20.6 ng/ml in non-smoker groups and the difference between the two groups was statistically significant (P value: 0.01).

The difference between the mean serum 25-hydroxyvitamin D level in patients with DM versus patients without DM (17.9 ± 21.4 versus 20.0 ± 11.8, P value: 0.45), in patients with history of hypertension versus patients without hypertension (21.0 ± 28.7 versus 17.44 ± 13.7, P value: 0.21) and in patients with dyslipidaemia versus patients without dyslipidaemia (20.5 ± 26.3 versus 17.0 ± 12.2, P value: 0.46) were not statistically significant.

In group A, five patients died during hospitalisation. The serum 25-hydroxyvitamin D level of one of them was 39 ng/ml. In other patients, the levels were 25, 21, 18 and 16 ng/ml. One patient with serum hydroxyvitamin D level of 18 ng/ml died within 30 days after discharge.

Discussion

Vitamin D is a hormone precursor. 1,25-Dihydroxyvitamin D is the mature hormone involved in regulation of mineral ion haemostasis [9].

Its receptors can be found in most tissues including heart muscle. Vitamin D has some important roles in maintaining normal function of muscles and immune system and controlling inflammation and cell proliferation [10].

The major source of vitamin D is cutaneous production. Ultraviolet radiation can change 7-dehydrocholesterol to vitamin D [6]. Synthesis of vitamin D in skin depends on many things including skin pigmentation, latitude, season, clothing, age, sunscreen use and local weather conditions [1]. Vitamin D also can be absorbed from both animal and plant foods in the intestine [9].

Vitamin D enters the circulation and is converted to 25-hydroxyvitamin D in the liver. Measuring serum

25-hydroxyvitamin D is the most common screening test because it is the major storage form of vitamin D. Its half-life is around two to three weeks [7].

Currently a normal level of 25-hydroxyvitamin D is defined as a serum level of 30–76 ng/ml (75–190 nmol/l) [1].

1,25-Dihydroxyvitamin D that is generated in kidneys has the greatest affinity to vitamin D receptors. Low levels of 1,25-dihydroxyvitamin D do not mean vitamin D deficiency because it results from other causes especially renal failure [1].

There are many studies in favour of a major role for vitamin D deficiency for the occurrence of diabetes mellitus, hypertension, cancer and cardiovascular diseases [11–14].

In the present study, we found a considerably high prevalence of vitamin D deficiency in patients with acute coronary syndrome. This finding is similar to previous studies in other countries [15]. According to NHANES 2001–2004, vitamin D deficiency was more prevalent in persons with cardiovascular diseases and cardiovascular diseases were more common in adults with lower 25-hydroxyvitamin D [6].

Major risk factors of vitamin D deficiency include old age, obesity, dark skin, lack of exposure to sun and fat mal-absorption [8].

It is interesting that despite the relatively low latitude of Ahvaz and its warm climate with sunny days, the prevalence of vitamin D deficiency was not low in normal people and 41.7% of cases in control group had serum 25-hydroxyvitamin D levels of less than normal. On the other hand, our study was performed at seasons of autumn and winter when people spend more time outside and are exposed more to sun compared to summer and late spring. In addition, none of our cases had used sunscreen. They did not use vitamin D and calcium supplements. During summer, the temperature is too high. Hence, people usually use sunscreen and spend almost all daytime inside. In women, the type of dressing (hijab) can be another thing causing avoidance of sufficient sun exposure but in our study, there was no statistically significant difference between serum 25-hydroxyvitamin D level in men and women. Obesity is very common in this part of Iran and it may be one of the reasons causing low circulating 25-hydroxyvitamin D although the BMIs in our cases were not so high [1,15]. Air pollution and genetic factors are the other factors that may have a role in reducing skin vitamin D production in people living in Ahvaz.

It has been observed in many studies that the risk of coronary artery disease and myocardial infarction occurrence is higher in persons with vitamin D deficiency [8,16,17].

How can vitamin D deficiency play a role as a risk factor for coronary artery disease?

Vitamin D deficiency may contribute to cardiovascular disease by stimulating renin expression, cardiomyocytes and smooth muscle cells proliferation, secondary hyperparathyroidism and inflammation [6].

Vitamin D has some anti-hypertrophic effects, suppression effect on renin angiotensin system, modulatory effect on contractility and regulatory effect on extracellular matrix turnover. Also it inhibits vascular calcification, improves endothelial function and has anti-atherosclerotic effects. In addition, vitamin D is a coronary artery disease risk factor modulator [18]. Despite these data, it is not certain that vitamin D deficiency has a direct role in cardiovascular disease or it affects the cardiovascular system indirectly.

In our study, vitamin D deficiency was more common in the smoker groups and the effect of smoking on vitamin D metabolism may be one probable reason.

Although the significance of vitamin D deficiency in coronary artery disease is well established in many observational studies, the role of vitamin D supplementation on the risk of coronary artery disease is not clear. A large trial on the effect of vitamin D supplementation on cardiovascular events did not show any significant impact. [19] Two other studies showed that 1000 IU vitamin D supplementation per day could decrease cardiovascular risk moderately but it was not statistically significant [18].

25-Hydroxyvitamin D levels are lower in obese persons when compared with lean persons. The explanation may be due to lower levels of exercise and sunlight exposure and sequestering of 25-hydroxyvitamin D in adipose tissues [1,15]. Our study showed lower serum 25-hydroxyvitamin D levels in obese patients but this difference was not significant which may be due to the small number of study cohort.

Our data showed a higher systolic blood pressure in patients with hypovitaminosis D and this was in agreement with previous studies [12]. Increased intracellular calcium leading to decreased renin activity, suppression of renin promoter gene and alteration of the vascular smooth muscle cells sensitivity are the probable mechanisms of vitamin D in blood pressure regulation [20].

We did not find any relation between hypovitaminosis D and short-term mortality in patients with acute coronary syndromes. It can be related to the small number of our patients and should be assessed in larger studies.

In conclusion, vitamin D deficiency was present in most of the patients admitted with acute coronary syndrome in Ahvaz, Iran. Prospective studies with a large number of cases are needed to investigate the benefits of screening and treatment of this common vitamin deficiency.

Some limitations of our study need to be acknowledged. The major limitation of our present study may be represented by the small number of patients and enrolling cases only during autumn and winter. Also, we did not assess daily vitamin D and calcium consumption among patients and control groups. Another important limitation was the lack of an adequate control group. Because we selected the cases of control group among the patient's family members and medical staff, we should consider selection bias as an important limitation.

Conclusion

Our data suggest that vitamin D deficiency was present in most of the patients admitted with acute coronary syndrome. This deficiency was more severe in patients with STEMI. We did not find any relation between vitamin D

deficiency and short-term mortality in patients with acute coronary syndrome.

Conflict of interest

None declared.

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